

**NEUROBIOLOGY**  
*for*  
**CLINICIANS**

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# THE BRAIN

- **IS NOT RATIONAL**
  - IT MAKES DECISIONS THROUGH EMOTIONS
  - IF LOSE CAPACITY TO HAVE EMOTIONS CAN NOT EVEN INITIATE A TASK (ANTONIO DAMASIO)
    - MIGHT STARE AT TOOTHBRUSH WITH TOOTHPASTE ON IT
- **DOES NOT MULTITASK**
  - DELUSION IS WE WILL GET MORE THINGS DONE IF WE DO MORE THAN ONE THING AT A TIME

# **THE BRAIN**

- **DOES NOT MULTITASK (CONTINUED)**
  - **MAY FLIP BACK AND FORTH BETWEEN TWO THINGS BUT STILL MISS MORE THAN WE WOULD IMAGINE**
- **IS A PATTERN-MAKER NOT A TRUTH-MAKER**
  - **TRIES TO FIT EVERYTHING INTO RECOGNIZABLE PATTERNS**
  - **SEEKS WHAT IS KNOWN AS OPPOSED TO WHAT IS UNKNOWN**

# **NEUROPLASTICITY**

- **BRAIN AT ALL AGES IS RESPONSIVE TO ENVIRONMENTAL STIMULI**
- **SYNAPSES CAN CHANGE IN MINUTES WHEN STIMULATED**
- **NEUROPLASTICITY IS MODULATED BY**
  - **GENETIC FORCES**
  - **EPIGENETIC FORCES**
- **THESE FACTORS INFLUENCE THE EXPRESSION OF GENES WITHOUT CHANGING THE DNA SEQUENCE**

# **NEUROPLASTICITY**

- **EPIGENETIC CHANGES ARE POTENTIALLY REVERSIBLE**
- **BRAIN IS VERY SENSITIVE TO SOCIAL STIMULI**
- **SOCIAL STIMULI (PARENTING, STYLE, EARLY STRESS, ETC.) CAN EPIGENETICALLY MODIFY THE EXPRESSION OF GENES THAT INFLUENCE BRAIN STRUCTURE AND FUNCTION (INCLUDING SENSITIVITY TO STRESS)**

# **NEUROPLASTICITY**

- **PREVENTION BASED ON IMPROVED PARENTING STYLE REDUCED RISK OF SUBSTANCE ABUSE IN ADOLESCENTS WITH A PARTICULAR VARIANT OF A GENE THAT RECYCLES SEROTONIN BACK INTO THE NEURON**
  - **THIS VARIANT IS VERY SENSITIVE TO SOCIAL ADVESITY**

# **NEUROPLASTICITY**

- **FOUR VARIANTS (GRAFMAN IN “THE BRAIN THAT CHANGES ITSELF.” DOIDGE, 2007)**

## **“MAP EXPANSION”**

**PLASTICITY AT BOUNDARY BETWEEN BRAIN MAPS**

## **“SENSORY REASSIGNMENT”**

**WHEN SENSE IS BLOCKED OR LOST ANOTHER SENSE CAN UTILIZE THE NEURAL SPACE**

## **“COMPENSATORY MASQUERADE” (COMPENSATION)**

**REDUNDANT BRAIN ALLOWS FOR MORE THAN ONE WAY TO ACCOMPLISH TASK**

## **“MIRROR REGION TAKEOVER”**

**WHEN ONE HEMISPHERE FAILS THE MIRROR REGION IN THE OTHER HEMISPHERE ADAPTS**

# **NEUROPLASTICITY**

- **BRAIN DERIVED NEUROTROPHIC FACTOR (BDNF)**
  - **WHEN AN ACTIVITY REQUIRES SPECIFIC CONNECTIONS BETWEEN NEURONS, BDNF CONSOLIDATES THE CONNECTION**
  - **BDNF PROMOTES THE MYELINATION OF NEURONS**
  - **DURING CRITICAL PERIODS BDNF TURNS ON THE NUCLEUS BASALIS, A PART OF THE BRAIN THAT FOCUSES ATTENTION AND KEEPS IT FOCUSED THROUGHOUT THE ENTIRE CRITICAL PERIOD**

# **NEUROPLASTICITY**

- **BRAIN DERIVED NEUROTROPHIC FACTOR (BDNF)**
  - **THE NUCLEUS BASALIS IS THE MODULATORY CONTROL CENTER FOR PLASTICITY**
    - **EXAMPLE-LANGUAGE HAS A CRITICAL PERIOD FROM INFANCY TO 8/PUBERTY. DURING THIS PERIOD LANGUAGE IS EASY TO LEARN. AFTER THE CRITICAL PERIOD IT TAKES SOMETHING NOVEL, IMPORTANT, SURPRISING OR IF ONE MAKES THE EFFORT TO PAY CLOSE ATTENTION**
  - **BDNF HELPS CLOSE DOWN THE CRITICAL PERIOD ONCE THE MAIN NEURAL CONNECTIONS ARE IN PLACE (STABILIZES SYSTEM)**

# **NEUROPLASTICITY**

- **BRAIN DERIVED NEUROTROPHIC FACTOR (BDNF)**
  - **THERE HAS BEEN AT LEAST A THREE FOLD INCREASE IN AUTISM IN THE LAST 15 YEARS ESPECIALLY IN CHILDREN EXPOSED TO A LOT OR CONSTANT WHITE NOISE (AIRPORT, SUBWAYS, INNER CITY TRAFFIC)- THESE CHILDREN ALSO HAVE LOWERED IQ**
    - **DURING AUDITORY CRITICAL PERIOD TOO MUCH STIMULATION CAUSES INCREASED BDNF RELEASE SHUTTING DOWN THE CRITICAL PERIOD AND LEAVING BRAIN MAPS POORLY DIFFERENTIATED**
    - **AUTISTIC CHILDREN DO PROCESS SOUND IN AN ABNORMAL WAY-THE UNDIFFERENTIATED MAP GETS TURNED ON BY ANY FREQUENCY CAUSING EXTREME SENSITIVITY TO SOUND AND POSSIBILITY OF EPILEPTIC SEIZURES**
    - **THE SAME PROBLEM MAY BE RELATED TO ATTENTIONAL DISORDERS**

# **NEUROPLASTICITY**

- **BRAIN MAPS**

- **PENFIELD (1930'S)**

- **SENSORY AND MOTOR BRAIN MAPS WERE TOPOGRAPHICAL MEANING AREAS ADJACENT TO EACH OTHER ON THE BODY SURFACE ARE ADJACENT TO EACH OTHER ON BRAIN MAP**

- **HUBEL AND WIESEL**

- **MICROMAPPED THE VISUAL CORTEX OF A KITTEN AND DISCOVERED DIFFERENT AREAS OF THE CORTEX PROCESSED LINES, ORIENTATION AND MOVEMENT. THE CRITICAL PERIOD WAS FROM 3-8 WEEKS AND REQUIRED STIMULATION FOR THE SYSTEM TO DEVELOP**

# NEUROPLASTICITY

- **BRAIN MAPS**

- **MERZENICH**

- **DISCOVERED THESE MAPS VARY IN THEIR BORDERS AND SHAPES BETWEEN INDIVIDUALS-THEY COULD CHANGE**
    - **ALSO TOPOGRAPHICAL ORDER EMERGES BECAUSE MANY OF OUR ACTIVITIES INVOLVE REPEATED SEQUENCES**

- **MERZENICH AND TALLAL (1996)-SCIENTIFIC LEARNING (FAST FORWARD)**

- **DISCOVERED CHILDREN WITH LANGUAGE DISABILITIES HAD AUDITORY PROCESSING PROBLEMS**
    - **WHEN ONE CANNOT HEAR ACCURATELY IT CREATES PROBLEMS IN VOCABULARY, COMPREHENSION, SPEECH, READING AND WRITING**

# EPIGENETIC CHANGES

- Do not “mutate” genes
- Mark genes in ways that alter how active they are
- Can last up to a lifetime
- Changes caused by drug use or chronic stress can change the way the brain responds to experience
  - Priming brain for resilience or to succumb to addiction

# **EPIGENETIC CHANGES**

- **Psychiatric disorders are precipitated in genetically susceptible individuals by environmental inputs (nature and nurture)**
- **Neurotransmitters can activate or inhibit nerve cells and switch “on” or “off” responsive genes**
  - **This helps determine how a nerve cell will respond and ultimately shapes behavior**

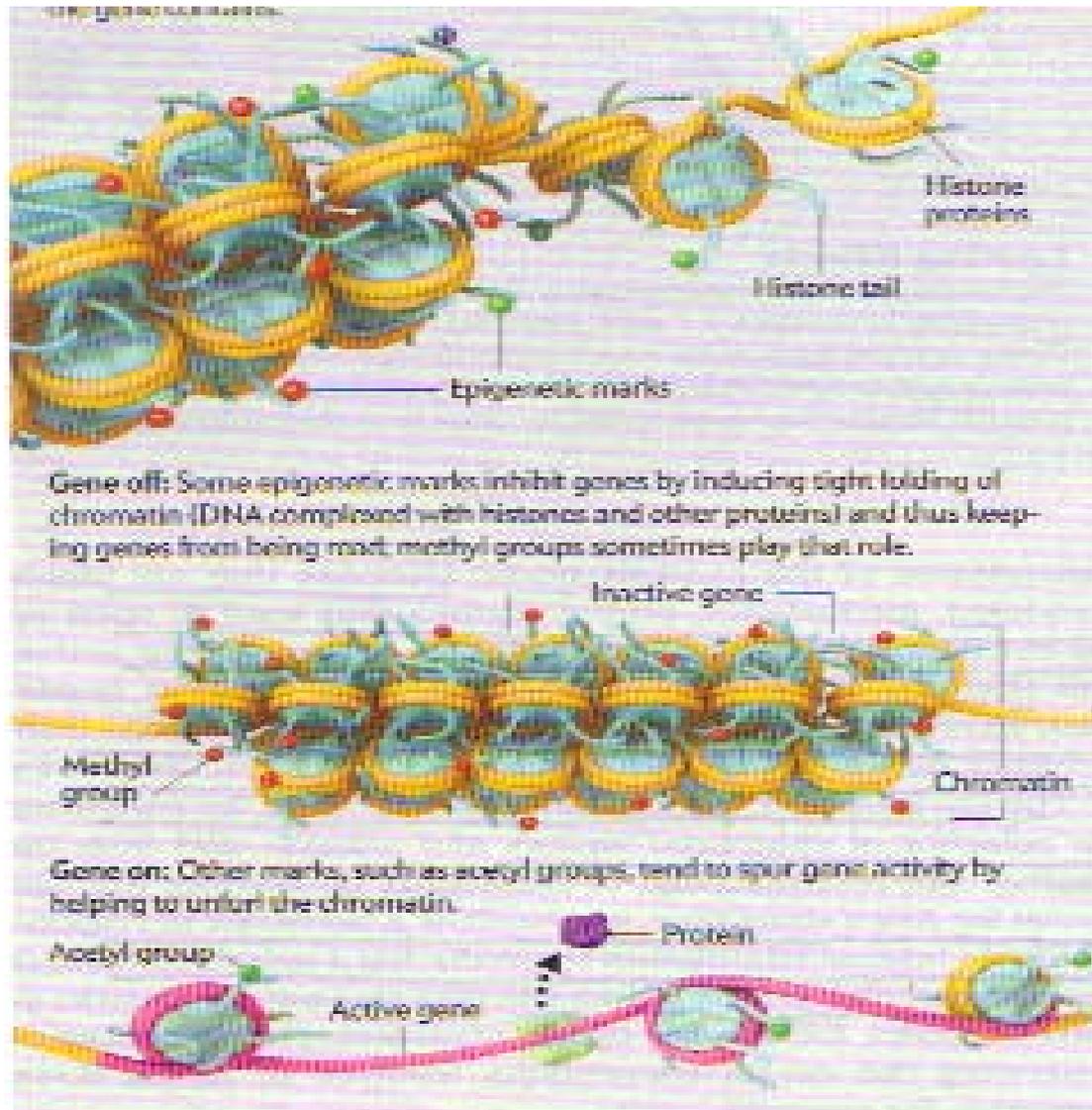
# EPIGENETIC CHANGES

- **How gene activity is regulated**
  - A gene is a stretch of DNA that specifies the make-up of a protein
  - Proteins carry out most processes in cells and this controls all cell behavior
  - DNA is wrapped around clusters of proteins called *histones* and further bundled into chromosomes

# EPIGENETIC CHANGES

- **The packaging of DNA helps regulate gene behavior**
  - **Tight packing tends to keep gene in an inactive state**
  - **When gene is needed it unfurls making the DNA available for transcription of DNA into RNA**
    - **RNA serves as a template for producing the encoded protein**
  - **Whether relaxed or tight is influenced by genetic markers (chemical tags attached to a histone or DNA)**

# EPIGENETIC CHANGES



# EPIGENETIC CHANGES

- **Epigenetic modifications are made by a variety of enzymes**
  - **Some of the enzymes add chemical tags and other enzymes remove tags**
    - **Called “writers” and “erasers”**
  - **Environment can influence gene activity by regulating the behavior of the “writers” and “erasers”**
    - **Addiction works in this manner**

# EPIGENETIC CHANGES

- **Drugs of abuse usurp the brains reward center**
  - **A single dose of cocaine switches on nearly 100 genes**
  - **Chronic use causes some genes to go silent (desensitization) but a much larger number have their levels boosted even higher (sensitized)**
    - **This “primes” the gene allowing them to remember rewarding effects (a set-up for relapse)**
      - **This loosens the structure of DNA so it is more prone to activity (i.e. increased sensitivity)**

# EPIGENETIC CHANGES

- **Drugs of abuse usurp the brains reward center (continued)**
  - **The loosened structure in addiction is caused by**
    - **Reducing activity of certain “erasers” that remove acetyl groups on histone**
    - **Reducing activity of certain “writers” that add inhibitory methyl groups**
    - **When more acetylated and less methylated the structure remains in a more open and relaxed state amenable to activation**

# EPIGENETIC CHANGES

- **Neural adaptations in depression**
  - Mild mannered mice paired with more aggressive mice (social defeat model)
  - After 10 days of being bullied the docile mice develop many signs of human depression (no enjoyment of sex or sweets, more anxious and withdrawn, listless)
  - Epigenetic modifications noted in around 2000 genes in the reward center
    - More histone methylation repressing gene activity

# EPIGENETIC CHANGES

- **Neural adaptations in depression (continued)**
  - **Depression may shut down genes important to activating reward center**
  - **Many of the changes can be reversed with an antidepressant (imipramine)**
  - **About one-third of male mice who were in the social defeat situation appeared to be resistant to depression**
  - **This suggests that an alternate pattern of epigenetic modification takes place that is positive (resilience)**

# EPIGENETIC CHANGES

- **Effects of maternal behavior mediated in part by epigenetic mechanisms**
  - **Pups of passive mothers show more DNA methylation than aggressively groomed pups in the regulatory sequence for a gene encoding the glucocorticoid receptor**
    - **This receptor mediates the response to cortisol**
  - **The excessive methylation in the hippocampus caused nerve cells to make fewer receptors**

# EPIGENETIC CHANGES

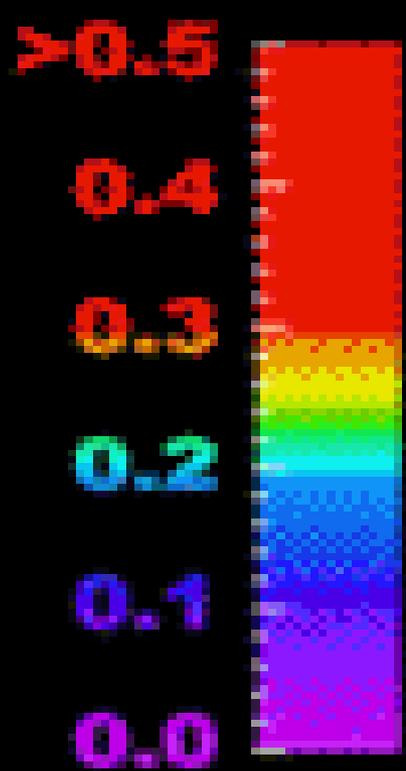
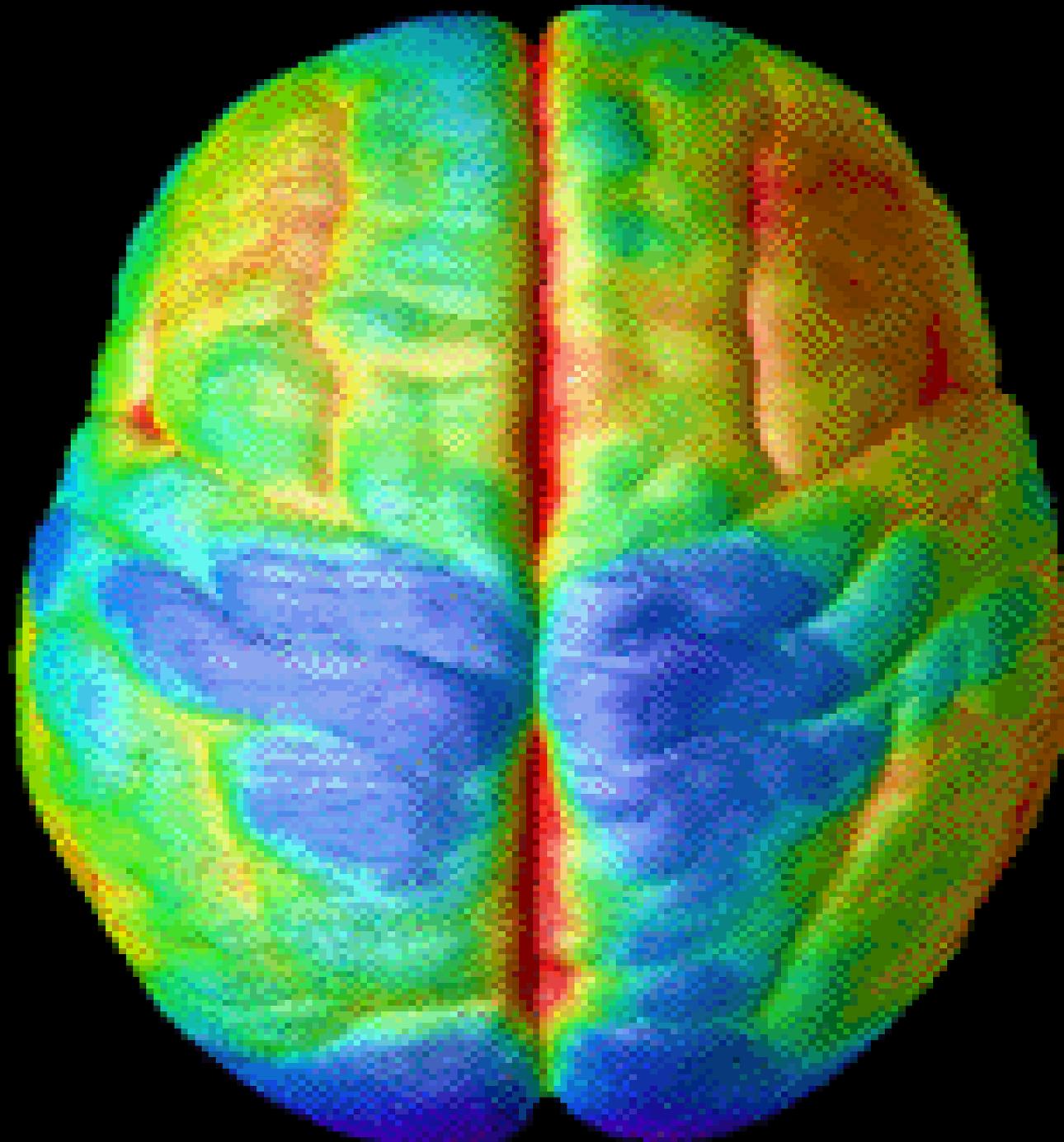
- **Effects of maternal behavior mediated in part by epigenetic mechanisms (continued)**
  - **Because activation of glucocorticoid receptors in the hippocampus signals the body to reduce production of cortisol, the epigenetic reduction in receptor numbers exacerbated the stress response making them more anxious and fearful**
    - **These traits lasted a life time**

# EPIGENETIC CHANGES

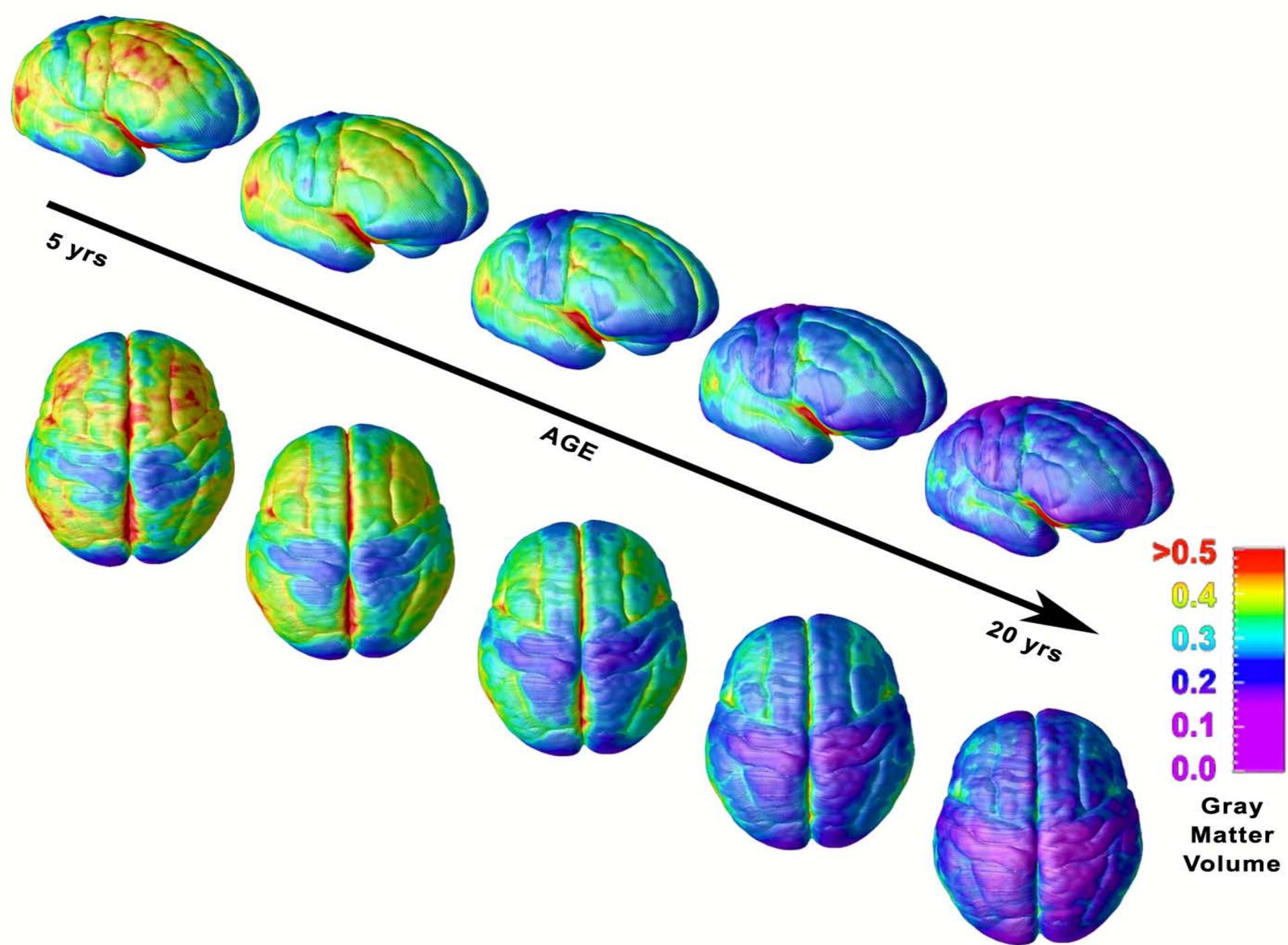
- **To what degree are these epigenetic changes heritable?**
  - Acquired epigenetic modifications are erased during the type of cell division that gives rise to sperm and egg cells
  - If parents exhibit certain behavioral patterns (active or passive, etc.) these can influence the offspring
  - May be more of a behavioral influence than the conveyance of genetic markers carved into the embryo
  - Nestler, Eric. *Hidden switches in the Mind*. Scientific American. December 2011. pgs. 77-83.

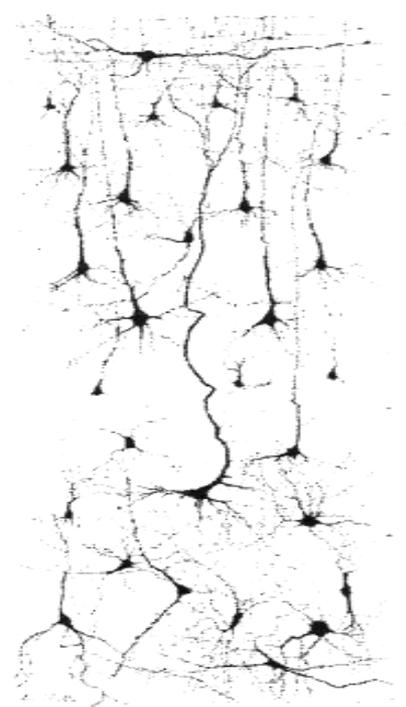
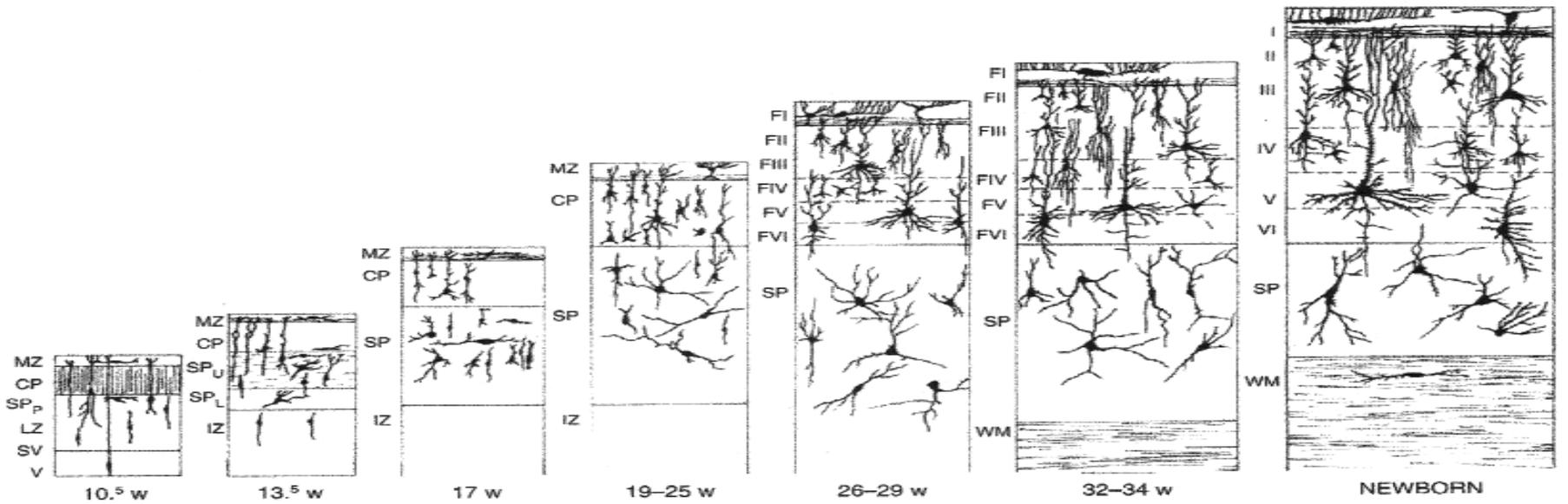
# BRAIN DEVELOPMENT

- Lower brain mostly born intact
- Prefrontal Cortex (PFC) plastic especially between 0-5 and 10-20 years of age
- PFC takes up to 25 years to develop
- *Developmental delays occur secondary to early life trauma and early onset alcohol/drug abuse.*
- PFC CRITICAL TO BECOMING RESILIENT



**Gray Matter  
Volume**

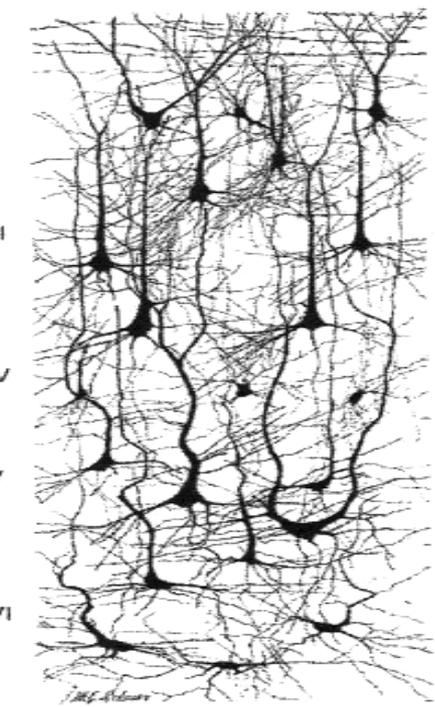




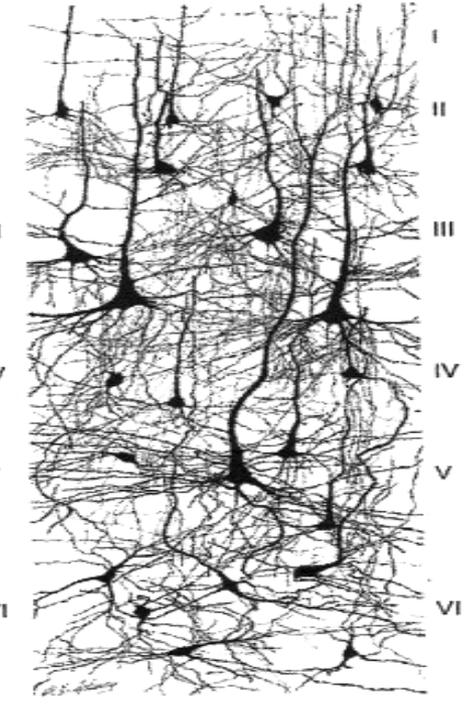
3 mo.



6 mo.



15 mo.



24 mo.

# RESILIENCE AND THE PFC

- WHAT CAN WE TREAT?

**Cognition**

**Affect**

**PEER AND PARENTAL  
RELATIONSHIPS**

# **Preadolescence & Adolescence Neurobiology Themes**

- **Brain cells, connectivity, receptors and neurotransmitters peak in childhood and are reduced during adolescence**
- **Connectivity among brain regions increases**
- **Balance between frontal (executive control) and limbic (emotional) systems changes**

# **Brain Cells, Connectivity, Receptors and Neurotransmitters**

- **Plasticity**
- **Competitive elimination**
- **Gray matter volume increases during childhood, declines through adolescence, level off during adulthood and then declines later in life**

# **Connectivity Among Brain Regions Increases**

- **Cognitive advances due to faster communication and increased integration**
- **Myelinated axons transmit impulses up to 100 times faster and decrease recovery time allowing a 30 fold increase in frequency**
- **Roughly equivalent to a 3000-fold increase in computer bandwidth**

# Balance Between Frontal and Limbic Systems Changes

- **Prefrontal Lobe circuitry increases**
  - **Some ability to delay gratification**
  - **Initial development of executive functioning**
    - **Problem solving**
    - **Abstraction**
    - **Conceptualization**
    - **Judgment**



# Modulation Ratio

**INHIBITION**

**EXCITATION**

# What Changes Modulation Ratio and Increases Risk of Anger and Aggression?

- Anything that  excitation in the lowers areas of the brain (brainstem and diencephalon)
- Anything that  inhibition in the areas of higher brain function (neocortex and limbic system)

# **CHILD AND ADOLESCENT DEVELOPMENT**

- **Puberty is starting earlier and the taking on of adult roles starts later**
- **Appears to be two crucial neural and psychological systems that interact to turn children into adults**
- **The developmental timing of these two systems has changed**
- **This has profoundly changed what we call adolescence**

# **CHILD AND ADOLESCENT DEVELOPMENT**

- **EMOTION AND MOTIVATION SYSTEM**

- Closely linked to the biological and chemical changes of puberty and involves the reward system (SEEKING SYSTEM)
- This system turns 10 year olds into restless, exuberant, emotionally intense teenagers (later it turns back in later placid adulthood)
- Recent studies (Casey at Cornell) suggest adolescents aren't reckless because they underestimate risk but because they overestimate rewards-or, rather find rewards more rewarding than adults (reward centers are very active in adolescence)

# **CHILD AND ADOLESCENT DEVELOPMENT**

- **EMOTION AND MOTIVATION SYSTEM**
  - Want social rewards-respect from their peers
  - Recent study (Steinberg at Temple University)
    - Teenagers did a high-risk driving task while lying in a fMRI machine.
    - The reward systems lighted up much more when they thought another teenager was watching-and they took more risks
  - Puberty not only turns on the motivational and emotional systems but also turns it away from family and toward the world of equals

# **CHILD AND ADOLESCENT DEVELOPMENT**

- **CONTROL SYSTEM (PREFRONTAL CORTEX)**
  - It channels and harnesses the energy
  - The prefrontal cortex **GUIDES OTHER PARTS OF THE BRAIN** including those that govern motivation and emotion
  - This system inhibits impulses, guides decision-making, plans for the long-term and delays gratification

# CHILD AND ADOLESCENT DEVELOPMENT

- **CONTROL SYSTEM (PREFRONTAL CORTEX)**
  - *This system is experience dependent*
  - It becomes more effective as we gain more SUPERVISED experience
  - EXPERTISE COMES FROM SUPERVISED EXPERIENCE
- These two systems were in sync in the past where farming and hunter-gatherer societies prevailed
- These societies created formal and informal apprenticeships

# **CHILD AND ADOLESCENT DEVELOPMENT**

- **In contemporary life, the relationship between these two systems has changed dramatically**
- **Puberty and the motivational system kicks in earlier**
- **At the same time contemporary children have very little experience with the kinds of tasks they'll perform as grown-ups**

# **CHILD AND ADOLESCENT DEVELOPMENT**

- *The experience of trying to achieve a real goal in real time in the real world is increasingly delayed and the growth of the control system depends on just those experiences*
- **As Ronald Dahl of UC-Berkeley states, “Today’s adolescents develop an accelerator a long time before they can steer and brake.”**

# CHILD AND ADOLESCENT DEVELOPMENT

- There is strong evidence that IQ has increased dramatically with children spending more time at school and even some evidence *higher IQ is correlated with delayed prefrontal lobe development*
- So students know more about a divergent number of topics but are not getting any kind of apprenticeship.
  - *Just learning the nature of heat and the chemical composition of salt does not make you a good cook*

# **CHILD AND ADOLESCENT DEVELOPMENT**

- **It could be said that children started their internships at age 7 not age 27**
- **There seems to be many young adults who are enormously smart and knowledgeable but directionless**
- **They are enthusiastic and exuberant but unable to commit to a particular kind of work or a particular love until well into their 20's or 30's**

# CHILD AND ADOLESCENT DEVELOPMENT

- *So faced with the uncompromising drive for sex, power and respect, these adolescents and young adults lack the expertise and impulse control necessary to successfully achieve within societal standards*
- **There are two facts about the brain important to remember**
- **First, experience shapes the brain**

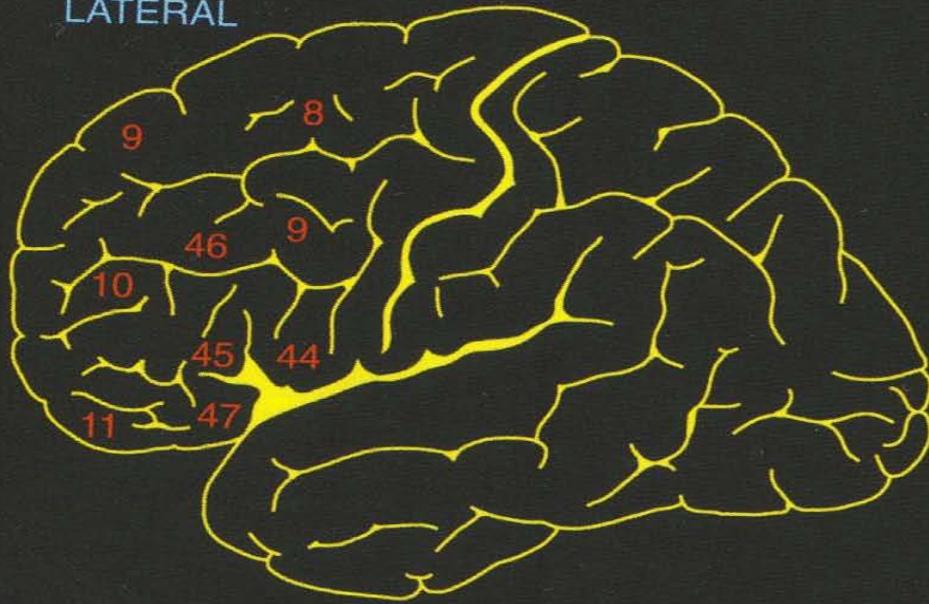
# **CHILD AND ADOLESCENT DEVELOPMENT**

- **It is as true to say our experience of controlling our impulses makes the prefrontal develop as it is to say the prefrontal makes us better at controlling impulses**
- **Second, development plays a crucial role in explaining human nature**
- **More and more evidence genes are just the first step in a complex developmental sequence involving interaction with the environment**

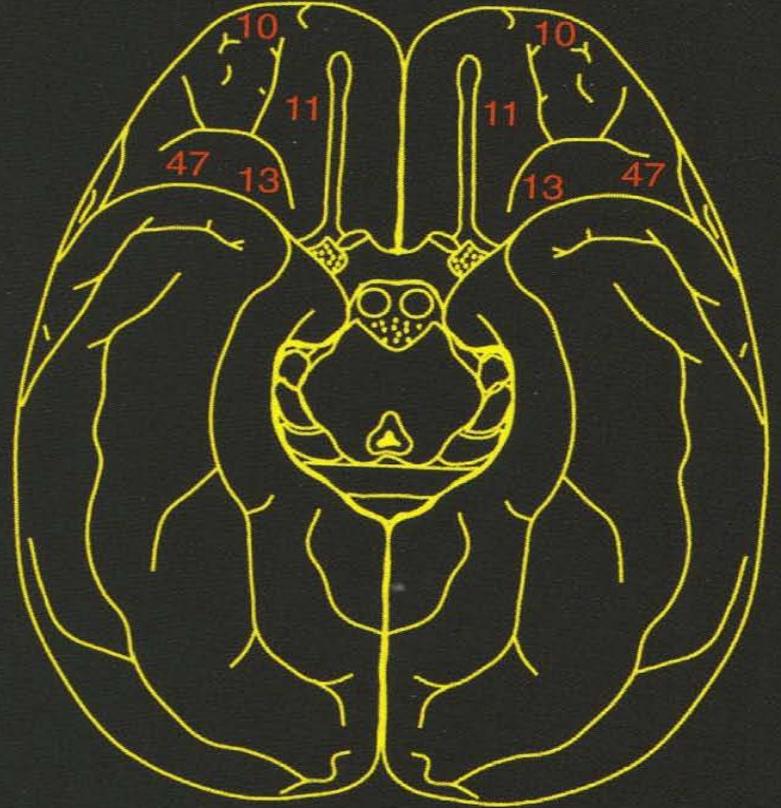
# **CHILD AND ADOLESCENT DEVELOPMENT**

- **It isn't that the adolescent/young adult brain just fails to show up**
- **It's that the prefrontal cortex is not properly instructed and exercised**
- **Because the brain is "plastic" it can respond to environmental stimuli**
- **Given the right stimuli this could help resolve some of the problems by helping to influence top-down control**

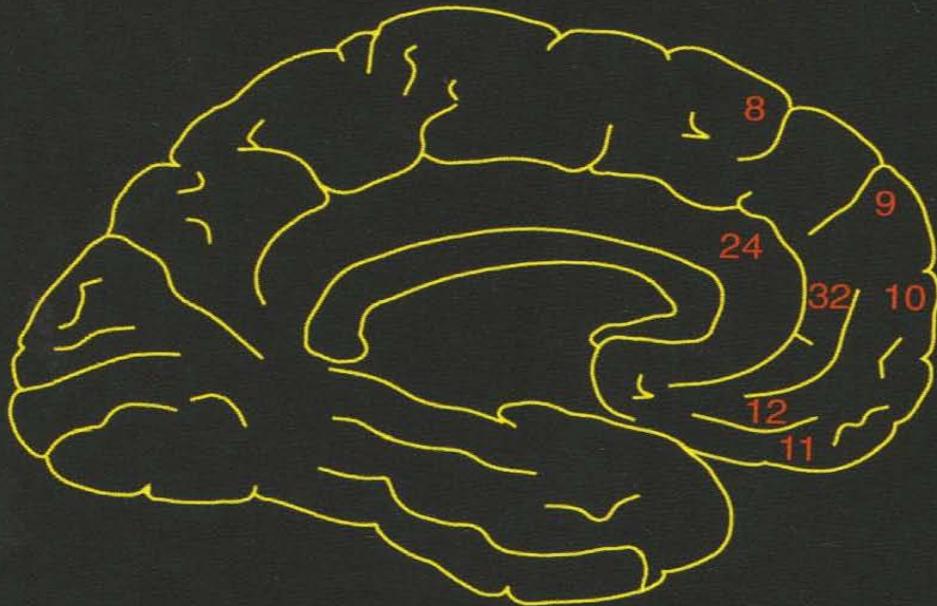
LATERAL

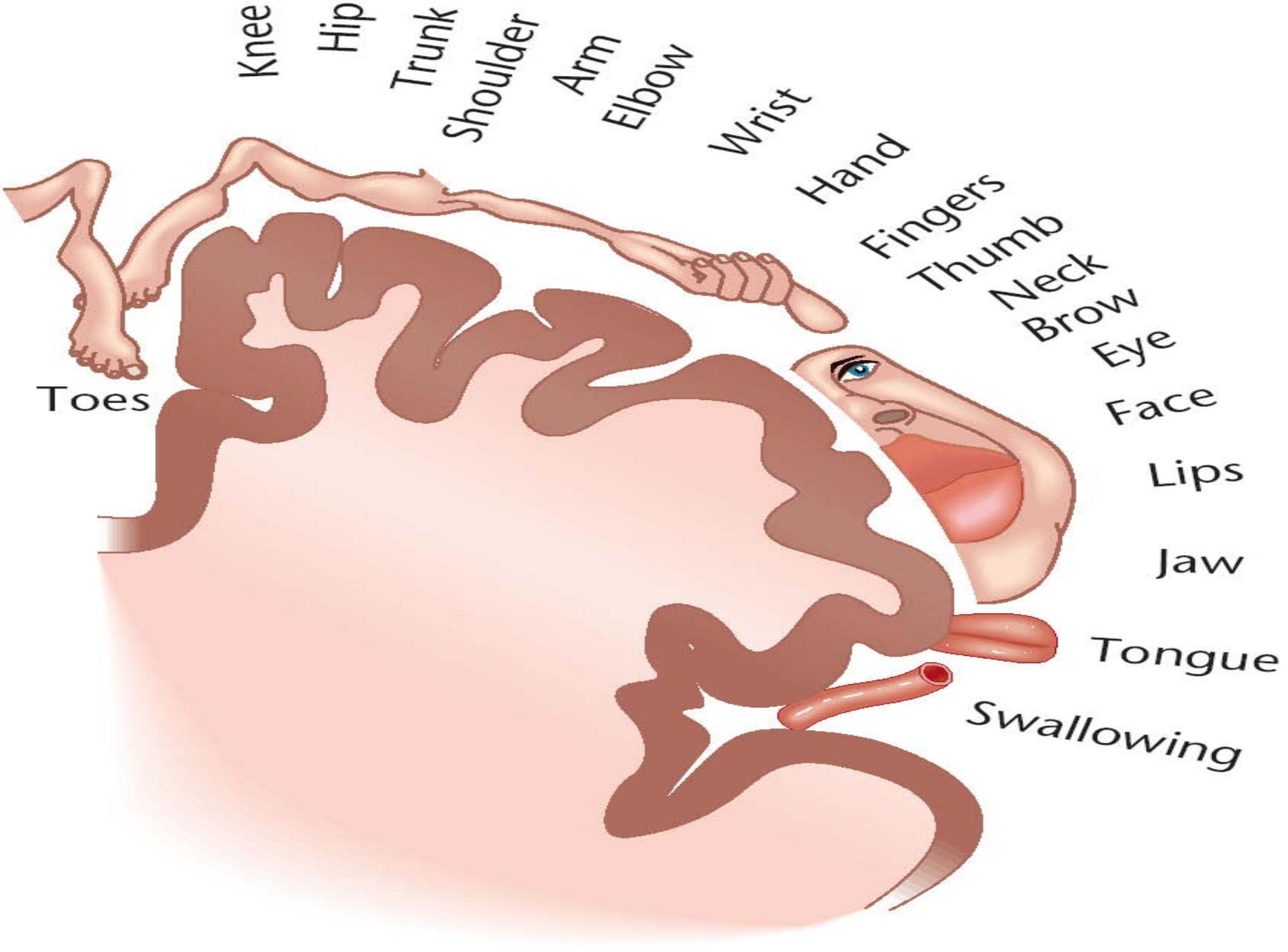


ORBITAL



MEDIAL / CINGULATE





Knee

Hip

Trunk

Shoulder

Arm

Elbow

Wrist

Hand

Fingers

Thumb

Neck

Brow

Eye

Face

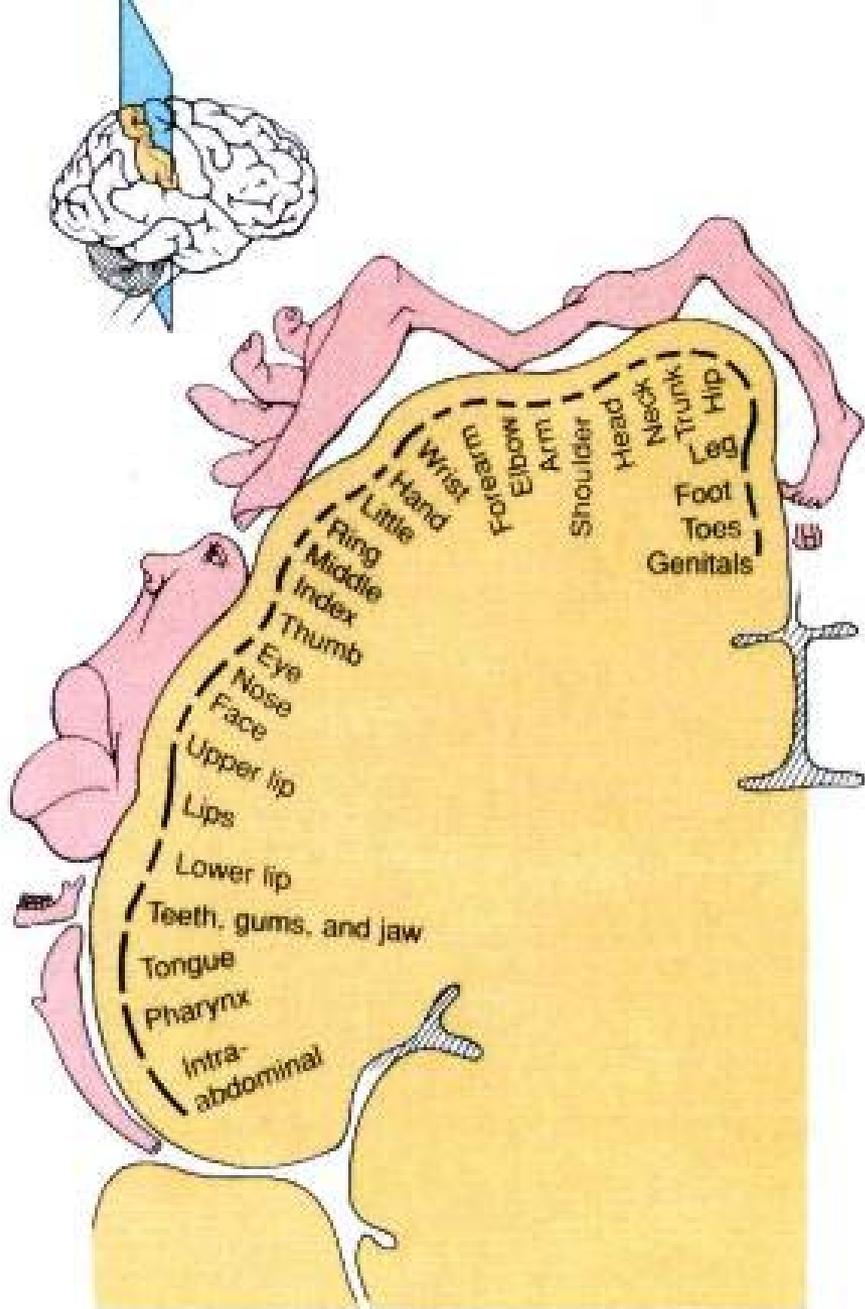
Lips

Jaw

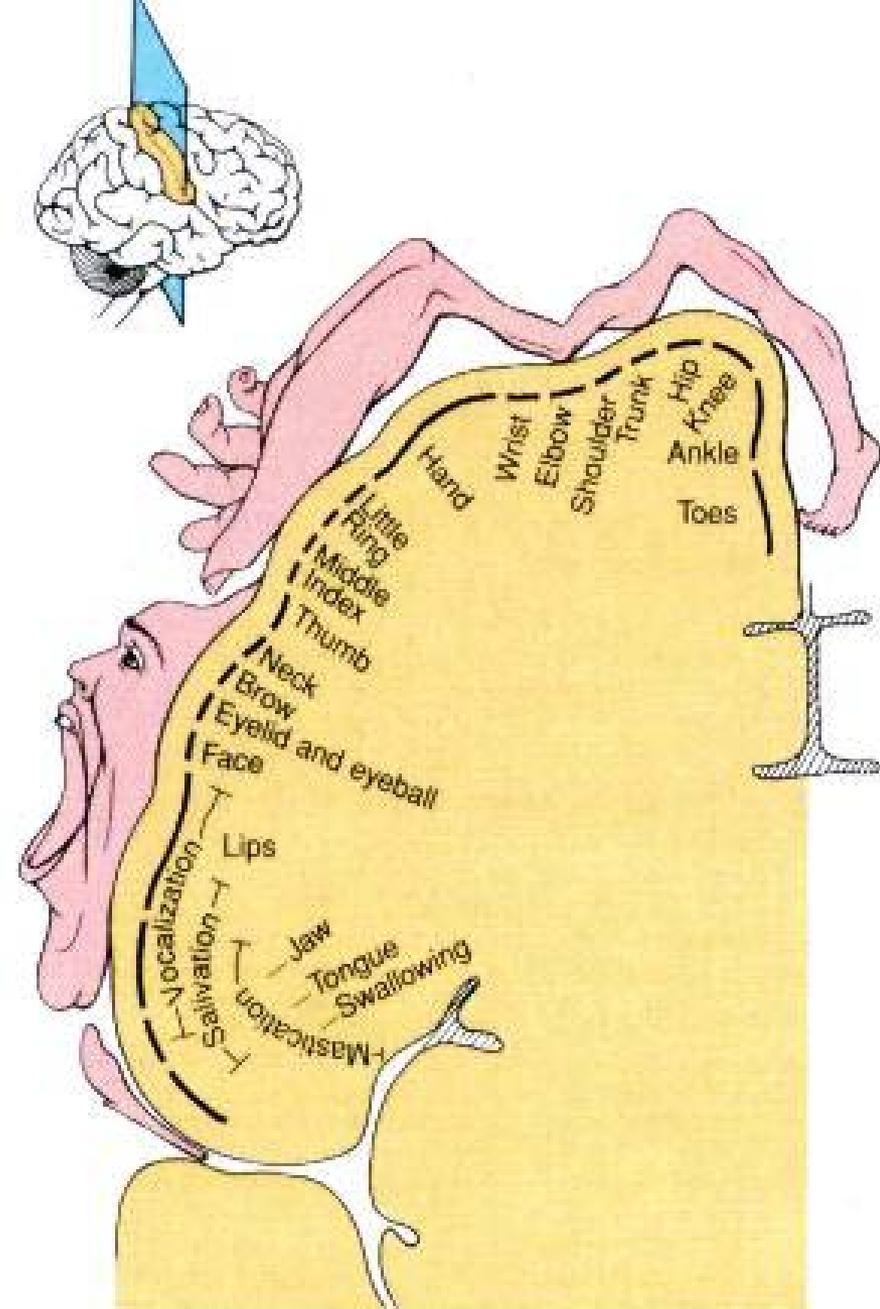
Tongue

Swallowing

Toes

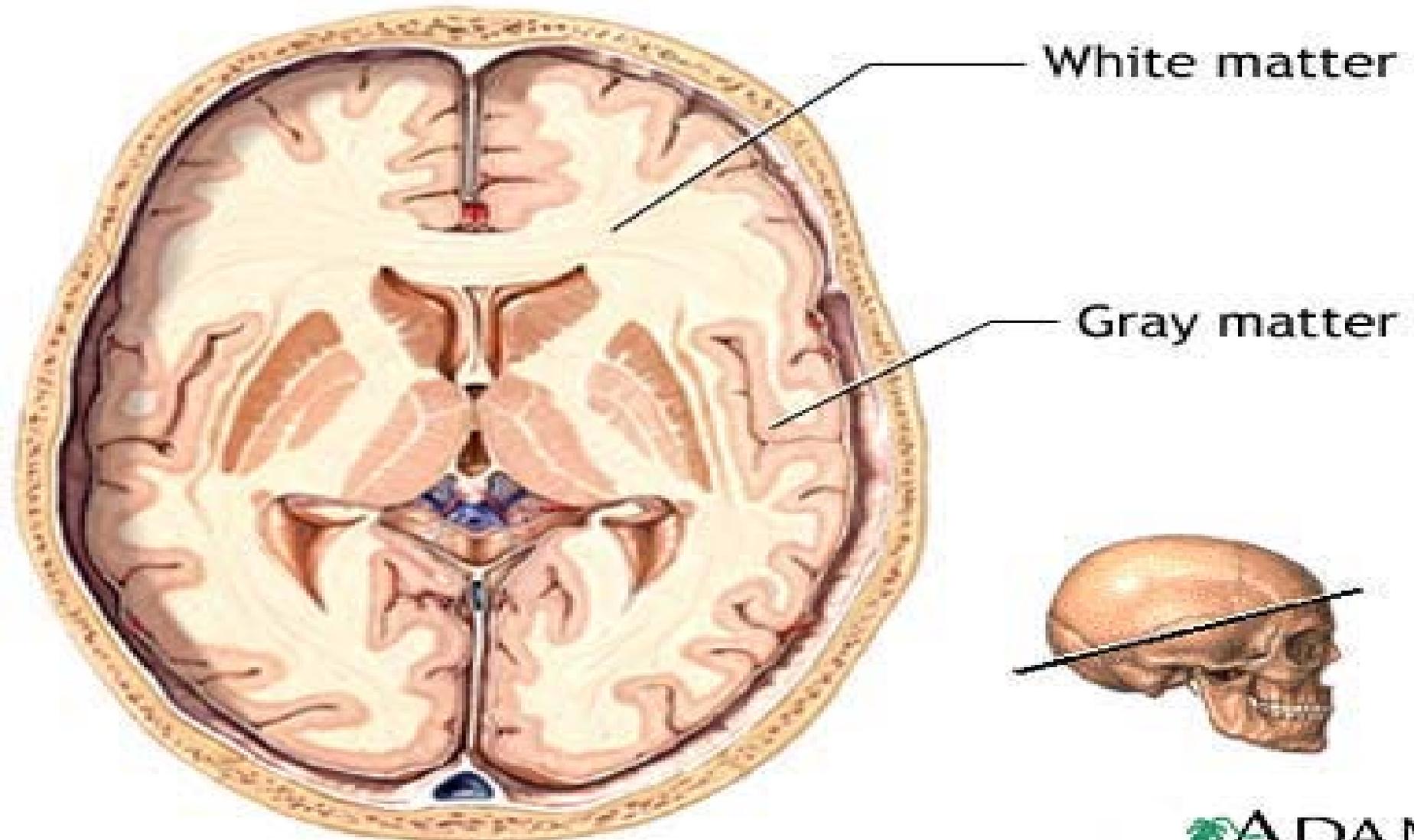


(a) Somatosensory cortex in right cerebral hemisphere



(b) Motor cortex in right cerebral hemisphere

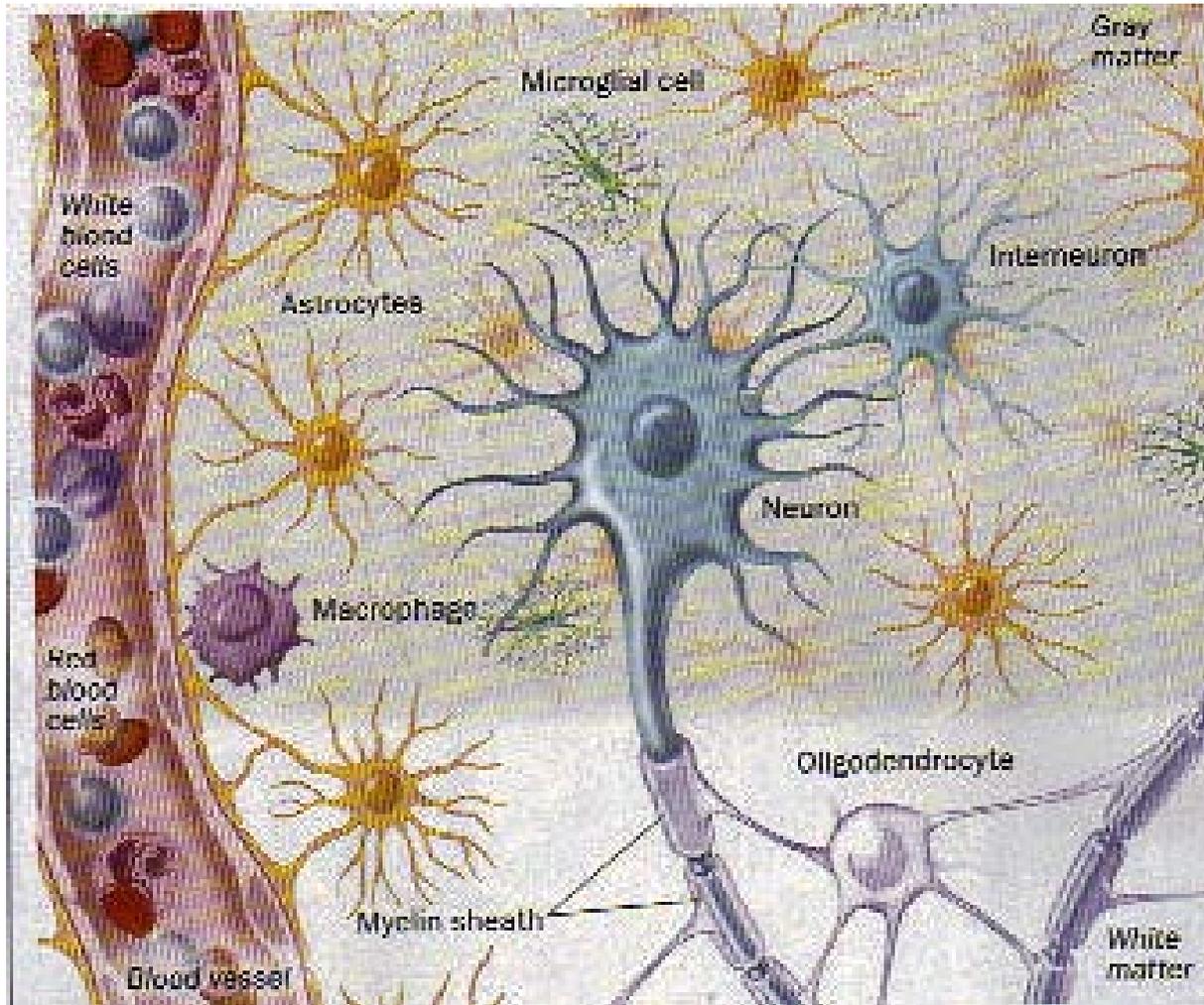
# WHITE MATTER



# **WHITE MATTER**

- **White matter is composed of bundles of myelinated axons**
- **White matter is often called the wiring of the brain because it connects individual neurons and groups of neurons together**
- **Amyloid plaques in white matter involved in neurodegenerative diseases**
- **Myelin degeneration found in Multiple Sclerosis**
- **Axonal shearing may be reversible**

# GLIAL CELLS



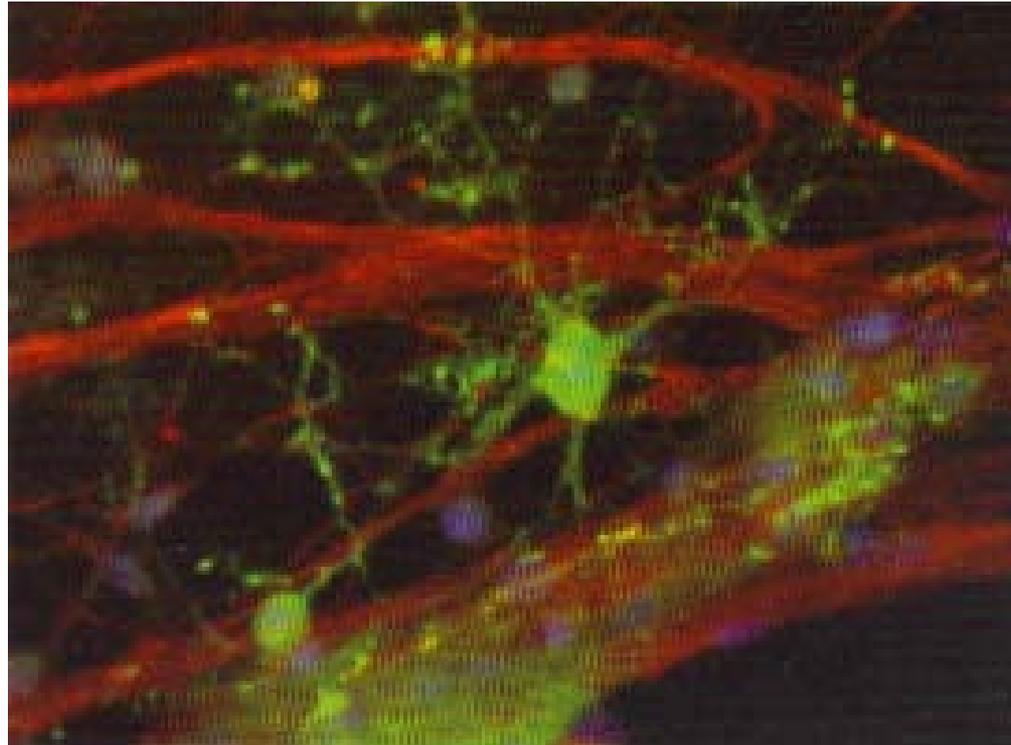
# **GLIAL CELLS**

- **NEURON DOCTRINE IS FLAWED**
- **SOME INFORMATION BYPOASSES NEURONS COMPLETELY FLOWING WITHOUT ELECTRICITY THROUGH NETWORKS OF GLIAL CELLS**
- **GLIAL CELLS INTERACT WITH NEURONS AND CONTROL THEM**
- **BRAIN IS COMPOSED OF 85% GLIAL CELLS AND 15% NEURONS**

# **GLIAL CELLS**

- **ASTROCYTES**
  - FERRY NEUROTRANSMITTERS, FOOD AND WASTE
  - CONTROL SYNAPTIC COMMUNICATION
- **OLIGODENDROCYTES**
  - WRAP THEMSELVES AROUND NEURONS LIKE SHEATHS (MYELIN) AND SPEED CONDUCTION BY UP TO 50 X'S
- **MICROGLIA**
  - FIRST RESPONDERS TO INJURY AND DISEASE KILLING INVADING GERMS AND INITIATING REPAIR

# GLIAL CELLS



# **GLIAL CELLS**

- **NEURONS ARE DEPENDENT ON GLIA TO FIRE ELECTRICAL IMPULSES AND TO PASS MESSAGES ACROSS SYNAPSES**
- **GLIA HAVE SAME NEUROTRANSMITTER (NT) RECEPTORS AS NEURONS**
- **WHEN NEURONS RELEASE NT SO DO GLIA**
- **GLIA NT RELEASE IMPACTS IMMEDIATE AND DISTANT SYNAPSES**

# **GLIAL CELLS**

- **DEMENTIA OF ALZHEIMERS COULD BE A DIRECT OUTCOME OF MICROGLIA THAT HAVE LOST THE ABILITY TO CLEAR WASTE**
  - **NORMALLY MICROGLIA DIGEST PROTEIN THAT FORM AMYLOID PLAQUES**
- **MICROGLIA INVOLVED IN SOME CHRONIC PAIN PATIENTS WHERE PAIN DOES NOT RELENT AFTER HEALING**
  - **MICROGLIA AND ASTROCYTES RELEASE CHEMICALS THAT PROMOTE HEALING**
  - **THESE CHEMICALS STIMULATE NEURONS**
    - **INITIALLY BENEFICIAL BECAUSE INCREASED PAIN AND SENSITIVITY CAUSE US TO PROTECT INJURED AREA**
    - **IN CHRONIC PAIN MICROGLIA DO NOT STOP RELEASING THESE CHEMICALS**

# **GLIAL CELLS**

- **INVOLVED IN DEMYELINATING DISORDERS SUCH AS MULTIPLE SCLEROSIS**
- **MICROGLIA RELEASE CYTOKINES LINKED TO OCD**
  - **HOXB8 GENE ASSOCIATED WITH COMPULSIVE GROOMING AND HAIR REMOVAL IN MICE SIMILAR TO HUMAN OCD**
  - **ONLY CELLS IN BRAIN THAT HAVE THIS GENE IS MICROGLIA**

# **GLIAL CELLS**

- **POSTMORTEM BRAIN TISSUE ANALYSIS LINKS OLIGODENDROCYTES AND ASTROCYTES TO DEPRESSION AND SCHIZOPHRENIA**
  - **SEE REDUCED NUMBERS CONFIRMED BY MRI FINDINGS**
  - **ALL HALLUCINOGENIC DRUGS (LSD, PCP, ETC.) PRODUCE THEIR EFFECTS BY ALTERING LEVELS OF NTs IN SPECIFIC CIRCUITS**
    - **ASTROCYTES REGULATE NT LEVELS AT SYNAPSES**

# **SUPRACHIASMATIC NUCLEUS**

- **BRAINS MASTER CIRCADIAN CLOCK**
- **FOUND IN HYPOTHALAMUS**
- **CONTROLS SLEEP-WAKE CYCLE**
- **SCN CELLS ACTIVE DURING THE DAY AND SILENT AT NIGHT**
- **BEGINS TO DECLINE IN MIDDLE AGE**
  - **REDUCED ACTIVITY DURING THE DAY AND INCREASE DURING THE NIGHT**
    - **REDUCED AMPLITUDE**

# **SUPRACHIASMATIC NUCLEUS**

- **BEGINS TO DECLINE DURING MIDDLE AGE (CONTINUED)**
  - **DIFFICULTY SLEEPING**
  - **DIFFICULTY ADJUSTING TO TIME ZONES**
  - **DIFFICULTY WITH SHIFT WORK**
  - **REDUCED ALERTNESS WHEN AWAKE**
    - **IMPACTS MEMORY AND METABOLIC PROCESSES**

# **CONSCIOUS AND UNCONSCIOUS ASPECTS**

- **CONSCIOUS MIND OR BRAIN**
  - **PREFRONTAL CORTEX**
  - **ALSO CALLED THE SOCIAL BRAIN**
- **UNCONSCIOUS MIND**
  - **GENETIC AND SPECIES SPECIFIC**
  - **SURVIVAL ORIENTED**

# Unconscious

Homeostasis

Stereotypic  
Movements

Learned  
Movements

Neurotransmitter  
and Hormone  
Release

Autonomic  
Regulation

Responds to  
Generalized  
Features  
of objects

Responses  
are fast



# Conscious

Novel Movement  
Sequences

Can assume  
Voluntary control  
of some unconscious  
Processes

Neurotransmitter  
and Hormone  
Release

Autonomic  
Regulation

Can address  
Specific  
Detail

Responses  
can be slow

# THE PREFRONTAL CORTEX

- **Coordinate the many brain activities needed to utilize:**
  - ***Executive Functions***
    - Set goals
    - Make plans to attain those goals
    - Organize steps to carry out the plans
    - Ensure that desired outcomes are achieved
  - ***Conscience***
  - ***Pursue Reward Within the Law***

# THE PREFRONTAL CORTEX

- The *orbital and medial prefrontal cortex* is primarily connected with
  - Thalamus
  - Hypothalamus
  - Amygdala
  - Hippocampus
  - Temporal lobe
- Involved with *emotion and instinctive and affect-modulated* behavior

# THE PREFRONTAL CORTEX

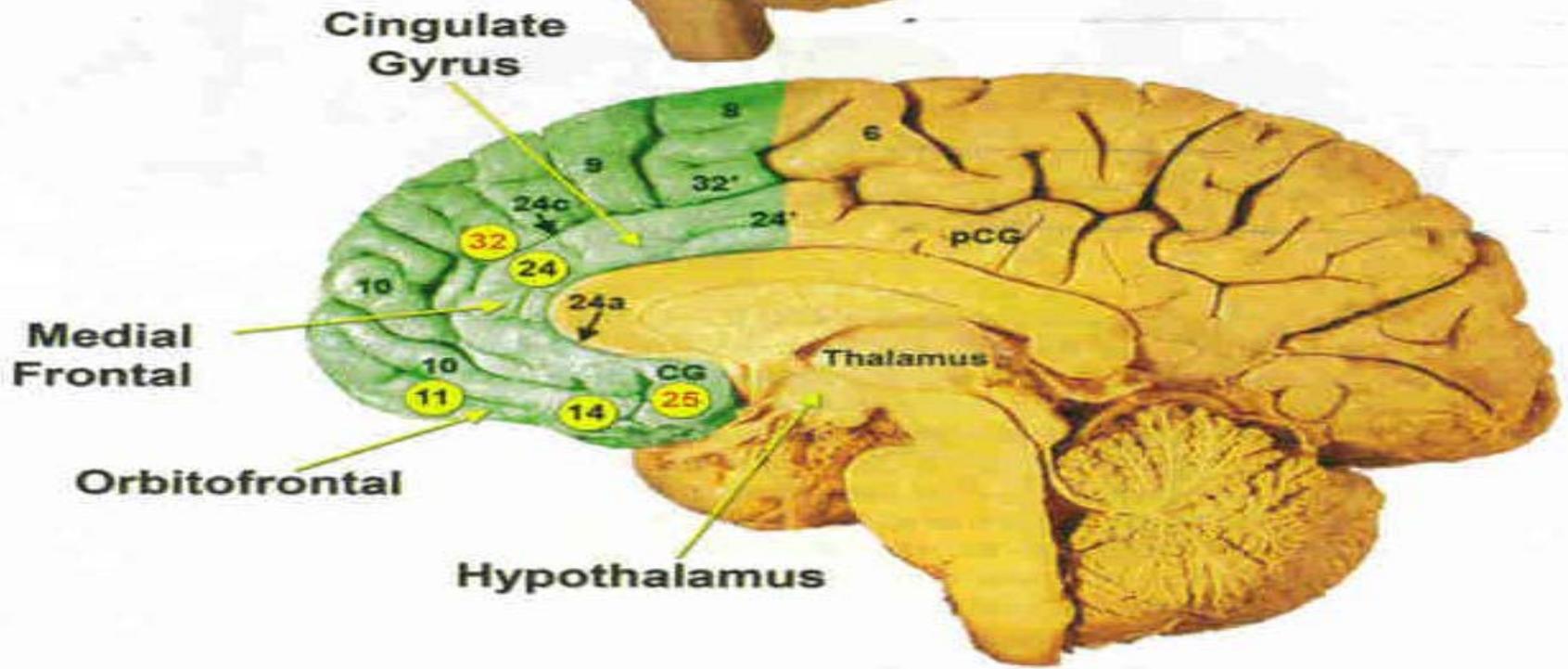
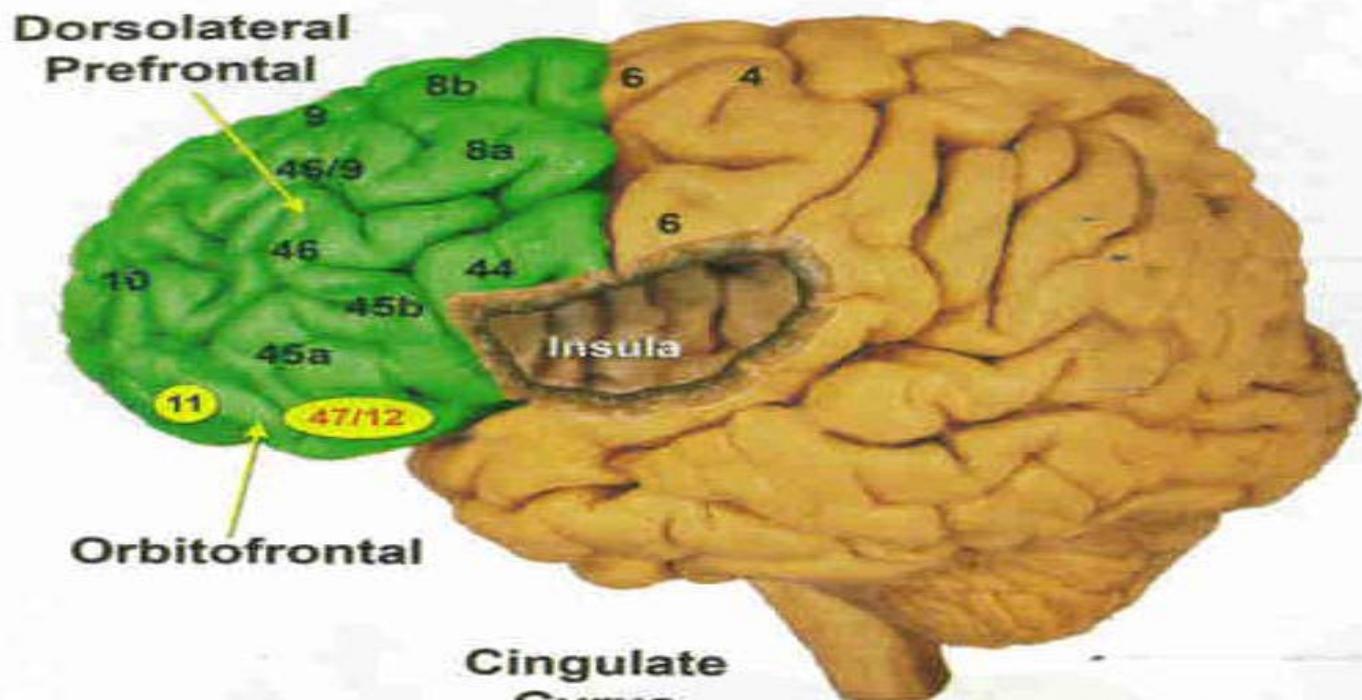
- The *lateral prefrontal cortex* is primarily connected with...
  - Thalamus
  - Caudate nucleus
  - Neocortex
- Constitutes the substrate for *executive functioning*

# THE PREFRONTAL CORTEX

- **Anterior Cingulate Cortex**
- **Orbitofrontal Cortex**
- **Dorsolateral Prefrontal Cortex**
- *Therapist task-optimize plasticity*

# **DORSOLATERAL PREFRONTAL CORTEX**

- **Entry point for verbal psychotherapy**
- **Essential for advanced reasoning**
- **Modulation of behavior thru use of words**



# **DORSOLATERAL PREFRONTAL CORTEX**

- **DORSOLATERAL PREFRONTAL CIRCUIT**
  - *Modulates Executive Functions*
    - Organization
    - Problem Solving
    - Working Memory
    - Memory Retrieval
    - Self-directedness
    - Ability to address novelty
    - Use of language to guide behavior

# Executive Functions

- ***Abstract Thinking***
  - Discerning relationships
  - “Seeing the forest for the trees”
- ***Attention Shifting***
  - Ability to shift attention when needed
- ***Information Manipulation***
  - Manipulate information in short-term memory

# Executive Functions

- ***Planning And Foresight***
  - Forming a mental model of a future event or situation
- ***Monitoring And Error Correction***
  - Engaged when results do not match intentions
- ***Decision Making***
  - Weigh options, arrive at a decision and see it through

# Executive Functions

- ***Inhibition***
  - Ability to inhibit impulses and delay gratification
- ***Social Functioning***
  - Appropriate processing of social cues

# **DORSOLATERAL PREFRONTAL CORTEX AND ADHD**

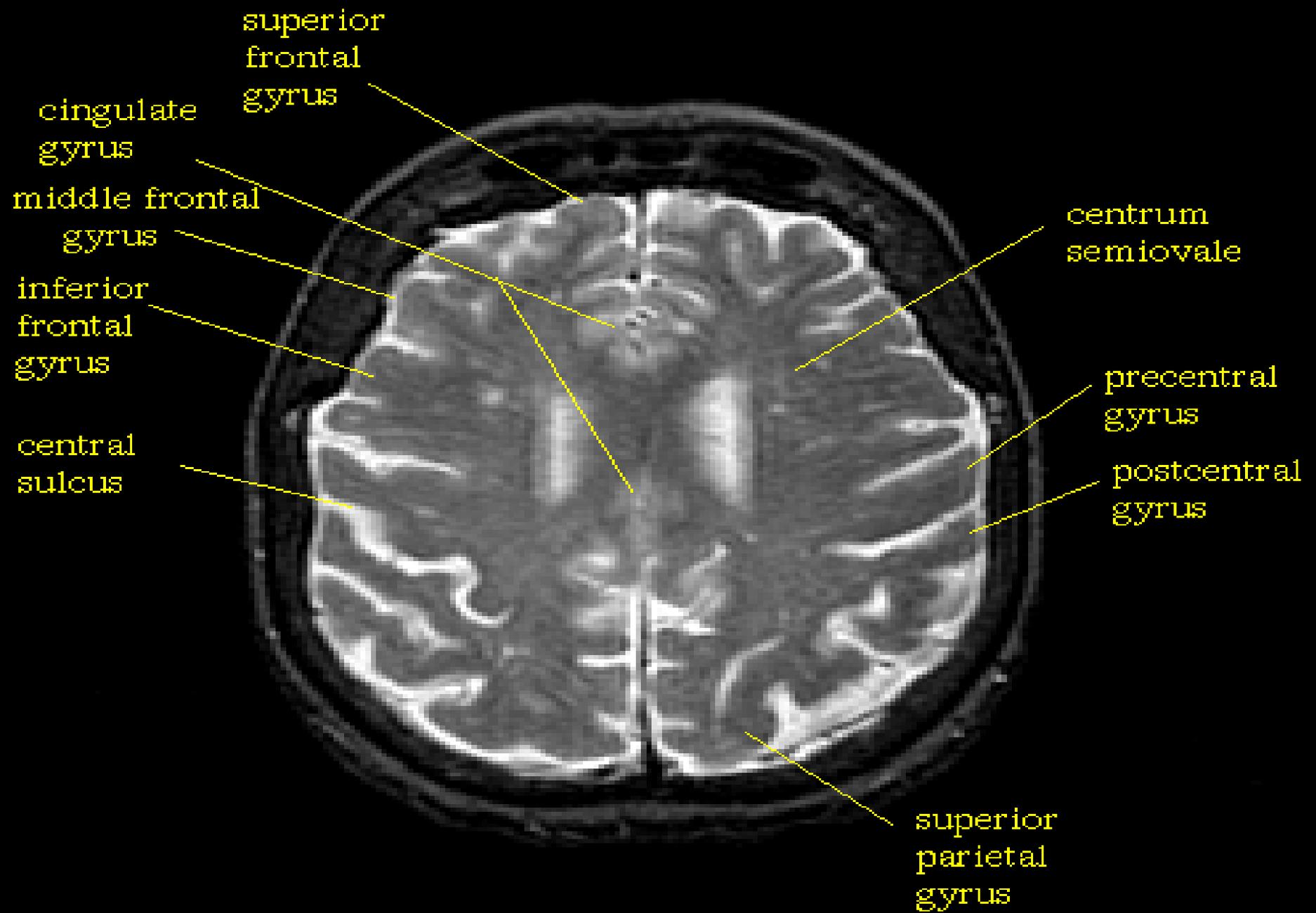
- It is the dorsolateral prefrontal cortex that most groups find is different in kids with ADHD. It's a bit smaller in volume. If you look at cortical thickness, it tends to be a bit thinner.
- The amygdala is very much associated with emotional processing. Some people have found differences, some haven't.

# DORSOLATERAL PREFRONTAL CORTEX AND ADHD

- One particularly interesting recent finding was that the connections between the amygdala and the frontal parts of the brain might be different in kids with ADHD.
- One particularly interesting study actually found that the hippocampus was bigger in kids who had ADHD. And, the fewer symptoms they had, the bigger the hippocampus, which might suggest that the hippocampus getting bigger is compensating for the symptoms.
- DRD4 gene-associated with brain development

# **ANTERIOR CINGULATE**

- ***ANTERIOR CINGULATE CIRCUIT***
  - Motivates goal-directed behavior
  - Conflict monitoring
  - Component of reward circuitry
  - Emotional-cognitive integration
  - Plays a part in experience of empathy
- **If damaged-Apathy**



# ANTERIOR CINGULATE

- **Coordinates**
  - *Maternal behavior*
  - *Nursing*
  - *Play*
- **Monitors personal, environmental and interpersonal information**
- **Helps regulate emotion and pain**
- **Allocates attention to whatever is most salient**

# ANTERIOR CINGULATE

- **Cocaine craving**
  - **Increases activation of the Anterior Cingulate which controls**
    - *Maternal behavior*
    - *Nurturance*
    - *Bonding*
- **Substance abusers may seek to satisfy intimacy needs by manipulating the neurobiology of attachment**

# **ANTERIOR CINGULATE**

- **Detection of errors**
- **Adjustment of response according to new information**
- **Clients with alexythymia (inability to experience or express feelings) have smaller anterior cingulate cortices**
- **Larger anterior cortices associated with worry and fearfulness**
- **Anterior cingulate has overlapping functions with other prefrontal cortices**

# SPINDLE CELLS

- IN ANTERIOR CINGULATE AND INSULA
- Spindle cells (VON ECONOMO CELLS) appear to play a central role in the development of *intelligent behavior* and *adaptive response to changing conditions* and *cognitive dissonance*. They become widely connected with diverse parts of the brain, indicating their essential contributions to the superior capacity of hominids to focus on difficult problems.
- Spindle cells emerge after birth and are experience-dependent
- *Early neglect and abuse negatively impact development causing deficits in anterior cingulate abilities*

# **SPINDLE CELLS**

- **AUTISM**

- **INVOLVES THEORY OF MIND WHICH EMERGES AROUND 4 YO**
- **IF CANNOT FIGURE OUT OTHER PEOPLE SOCIAL INTERACTIONS ARE BAFFLING**
- **DON'T LOOK AT THE OTHERS FACE, DON'T COPY. DON'T MIMIC AND DON'T YAWN WHEN OTHERS AROUND THEM DO**

# **SPINDLE CELLS**

- **AUTISM**

- **AREAS OF THE INSULA AND ANTERIOR CINGULATE WHICH ARE ACTIVATED BY SOCIAL INTERACTION ARE RELATIVELY INACTIVE IN AUTISM**
- **MAY INVOLVE SPINDLE NEURONS WHICH ARE FOUND ONLY IN THE TWO ABOVE AREAS**
- **THESE NEURONS KEEP TRACK OF SOCIAL EXPERIENCES AND PROVIDE BASIS FOR INTUITIVE SOCIAL LEARNING WHEN WE WATCH AND COPY OTHERS**
- **Scientific Am Mind. March/April 2011, pg 16-17.**

# ANTERIOR CINGULATE DEFICITS

- Decreased maternal behavior
- *Decreased empathy*
- Decreased emotional stability
- Disruption of Autonomic Nervous System (ANS) and Hypothalamic-Pituitary-Adrenal (HPA) functioning
- Increased response to stress
- Decreased expressiveness
- Inappropriate social behavior
- Impulsiveness

# ORBITOFRONTAL CORTEX

- **ORBITOFRONTAL CIRCUIT**
  - Modulates pursuit of reward
    - Risk
    - Context
    - Potential consequences
  - In conjunction with amygdala can stimulate or inhibit ANS
  - *If damaged-impulsivity, social inappropriateness, disregard for rules and consequences*

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# Obsessive Compulsive Disorder

- *More recent areas in PFC not affected*
  - Why the compulsions seem alien
  - Reasoning is intact
- **Develop a treatment plan that gives the mind a way to reprogram the brain**
  - Neuroplasticity
- **Problem is associative memory**
  - More succumb to obsessions and engages in compulsive behavior the stronger the neural network

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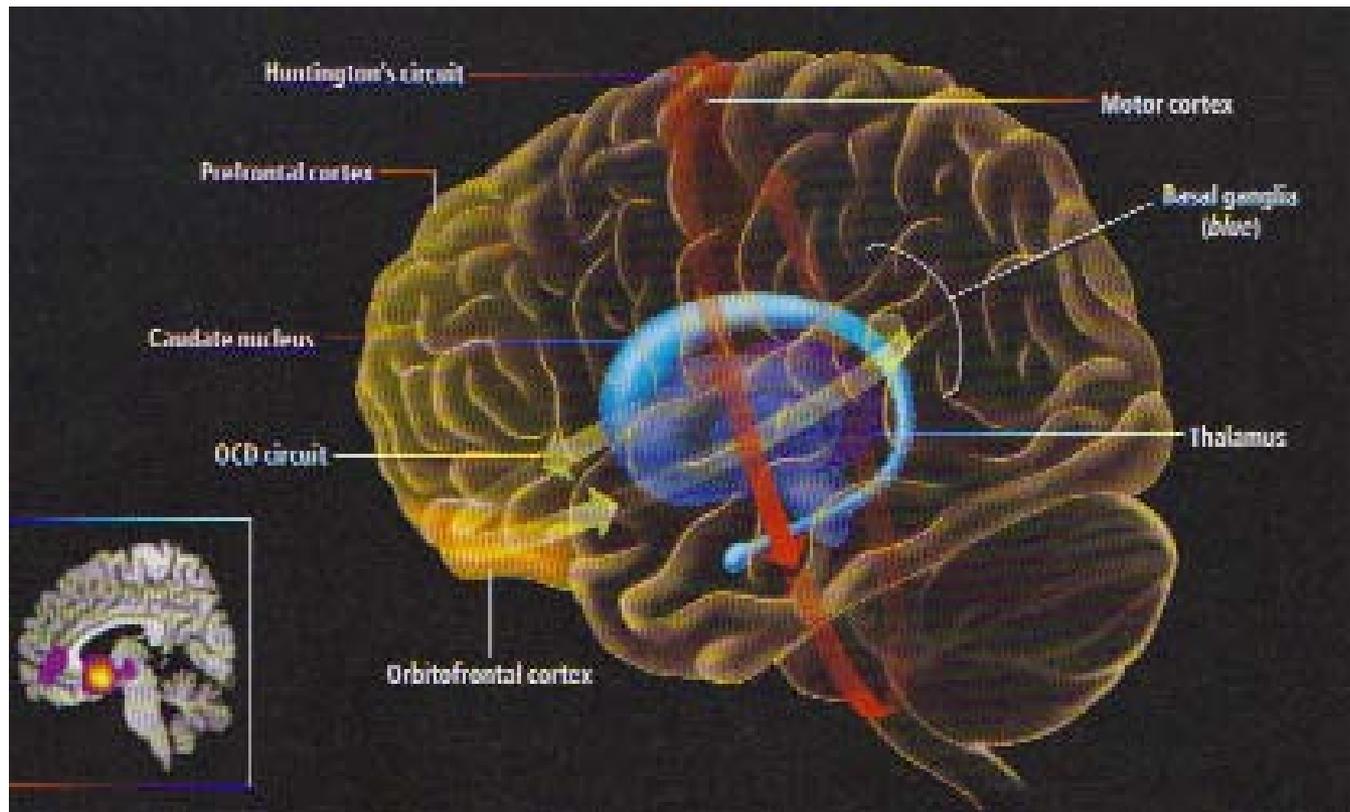
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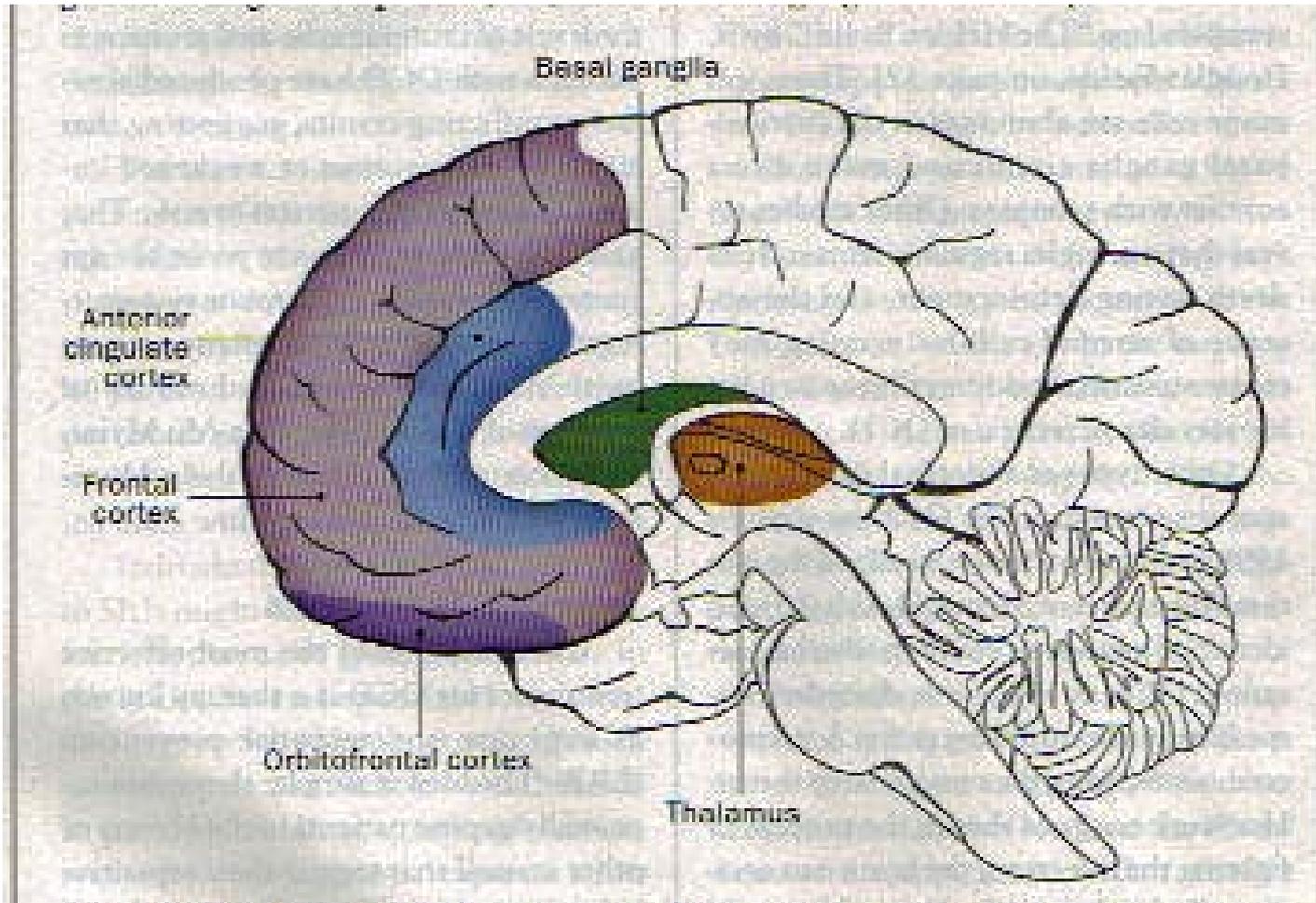
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# **SYMPTOMS RESIDE IN CIRCUITS**

- **Problems occur when networks do not communicate properly**
  - Neurotransmitters
  - Transporters or vesicles
  - Reuptake pumps
  - Receptors
- **Neural circuits in depression**

# OBSESSIVE-COMPULSIVE DISORDER CIRCUIT





# **OBSESSIVE-COMPULSIVE DISORDER CIRCUIT**

- **ORBITOFRONTAL CORTEX-A DECISION MAKING HUB**
- **BASAL GANGLIA-MEDIATES REWARD FEELINGS AND INITIATES BEHAVIOR**
- **THALAMUS-STIMULUS FILTERING**
- **ANTERIOR CINGULATE-MONITORS MISTAKES AND FOCUSES ATTENTION**

# **OBSESSIVE-COMPULSIVE DISORDER CIRCUIT**

- **INVOLUNTARY MOVEMENTS ORIGINATE IN THE BASAL GANGLIA, A GROUP OF STRUCTURES INVOLVED IN INITIATING AND COORDINATING BASIC MOTOR ACTIONS**
- **THE CAUDATE NUCLEUS OF THE BASAL GANGLIA IS A PART OF THE BRAIN CIRCUIT THAT DRIVES OCD ALONG WITH THE ORBITOFONTAL CORTEX, A REGION CRITICAL TO DECISION MAKING AND MORAL JUDGMENT AND THE THALAMUS WHICH RELAYS AND INTEGRATES SENSORY INFORMATION**
- **OCD SUFFERERS SHOW HYPERACTIVITY IN AREAS OF THE FRONTAL CORTEX AND THE BASAL GANGLIA**

# **OBSESSIVE-COMPULSIVE DISORDER CIRCUIT**

- **WHEN SYMPTOMS IMPROVE-EITHER BY PSYCHOTHERAPY OR MEDICATION-A DECREASE IN ORBITOFRONTAL CORTICAL ACTIVITY IS OBSERVED**
- **IN NON-RESPONSIVE PATIENTS DISCONNECTING THE ORBITOFRONTAL FROM THE CAUDATE NUCLEUS REDUCES SYMPTOMS IN SEVERE OCD**

# **OBSESSIVE-COMPULSIVE DISORDER CIRCUIT**

- **NORMALLY WHEN WE MAKE A MISTAKE**
  - **WE GET A “MISTAKE FEELING”-A NAGGING SENSE SOMETHING IS WRONG**
    - **OFC DETECTS MISTAKE**
    - **THE MORE ACTIVE THE OFC THE MORE OBSESSIVE THE PERSON IS**
  - **NEXT WE BECOME ANXIOUS-THIS DRIVES US TO CORRECT THE MISTAKE**
    - **ANTERIOR CINGULATE TRIGGERS THE ANXIETY THAT SOMETHING BAD WILL HAPPEN IF MISTAKE IS NOT CORRECTED**
    - **AC SENDS SIGNALS TO THE HEART AND GUT**

# **OBSESSIVE-COMPULSIVE DISORDER CIRCUIT**

- **NORMALLY WHEN WE MAKE A MISTAKE**
  - **WHEN THE MISTAKE IS CORRECTED AN AUTOMATIC “GEAR SHIFT” ALLOWS US TO MOVE ON-THE “MISTAKE FEELING’ AND ANXIETY DISAPPEAR**
    - **CAUDATE NUCLEUS IS THE “GEAR SHIFT”**
    - **IN OCD THE PAGE IS NOT TURNED AND THE “MISTAKE FEELING” AND THE ANXIETY INCREASE BECAUSE THE CAUDATE IS “STICKY”**
    - **ALL THREE AREAS BECOME HYPERACTIVE-A FORM OF “BRAIN LOCK”**

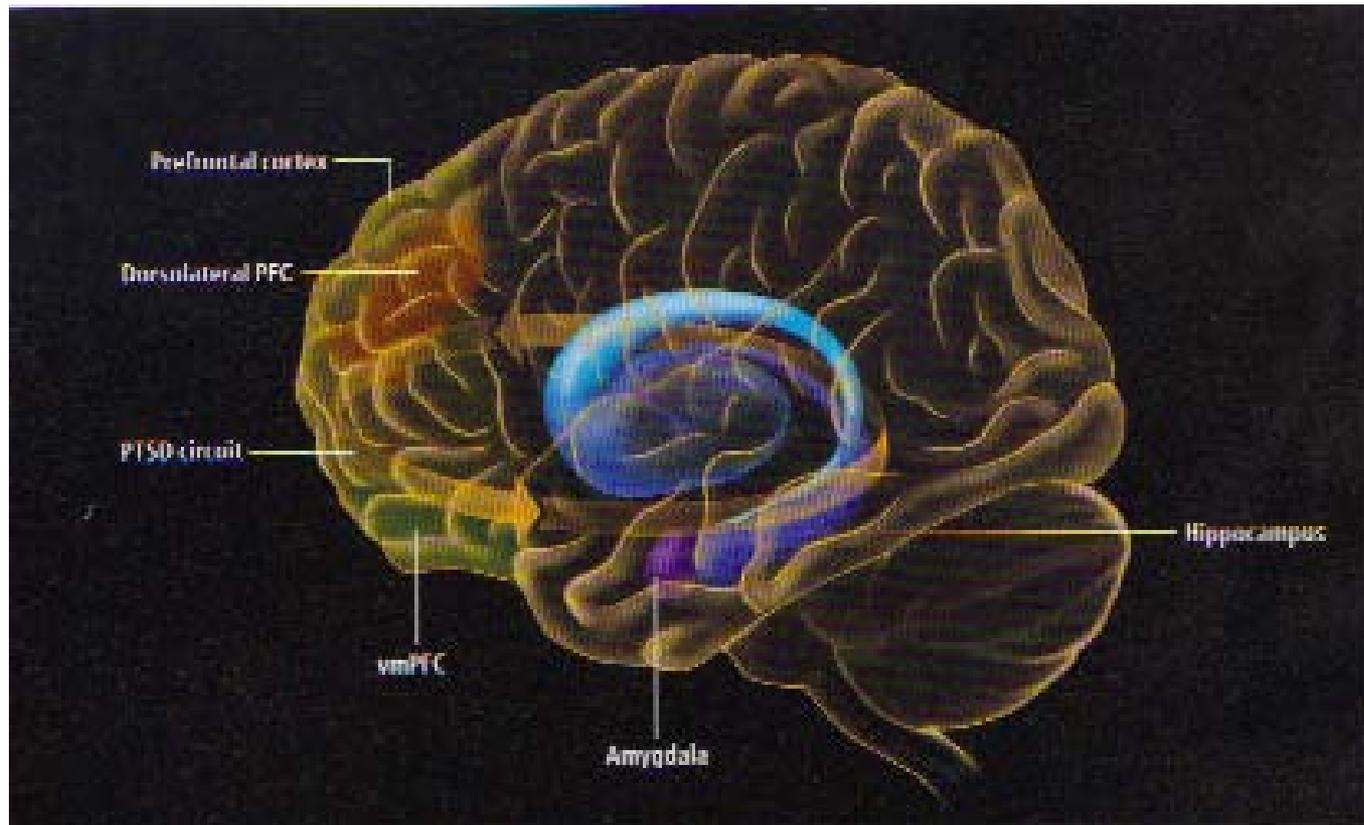
# **OBSESSIVE-COMPULSIVE DISORDER CIRCUIT**

- **MAY CONSIDER GETTING THE PERSON WITH OCD TO RELABEL WHAT IS HAPPENING**
  - **NOT AN ATTACK OF GERMS OR AIDS BUT AN EPISODE OF OCD**
  - **THIS CREATES SOME SEPARATION BY REMINDING THEMSELVES IT IS A FAULTY CIRCUIT**
  - **NEED TO DISTINGUISH BETWEEN THE FORM OF OCD (WORRISOME THOUGHTS AND URGES) AND THE CONTENT OF THE OBSESSION (DANGEROUS GERMS)**
    - **THE MORE ONE FOCUSES ON THE CONTENT THE MORE THE SYMPTOMS INCREASE**

# **OBSESSIVE-COMPULSIVE DISORDER CIRCUIT**

- **THEN HAVE THE PATIENT REFOCUS ON A POSITIVE, WHOLESOME IDEALLY PLEASURABLE ACTIVITY**
  - **EVERY MOMENT YOU THINK OF THE CONTENT YOU STRENGTHEN THE CIRCUIT**
  - **EVERY TIME YOU DO SOMETHING DIFFERENT YOU STRENGTHEN A DIFFERENT CIRCUIT**
    - **“the more you do it the more you want to”**
    - **“the less you do it the less you want to”**

# POST-TRAUMATIC STRESS DISORDER CIRCUIT



# **POST-TRAUMATIC STRESS DISORDER CIRCUIT**

- **MALFUNCTIONING OF THE VENTROMEDIAL PREFRONTAL CORTEX (vmPFC) IS THOUGHT TO INCREASE VULNERABILITY BECAUSE IT MODULATES THE AMYGDALA, A DRIVER OF FEAR AND ANXIETY**
- **NORMALLY EXTINCTION REPLACES A FEAR RESPONSE WHEN A NEUTRAL RESPONSE IS LEARNED BY THE HIPPOCAMPUS AND THE DORSOLATERAL PREFRONTAL CORTEX**
- **THE vmPFC IS BELIEVED TO SERVE AS THE CRITICAL LINK BETWEEN THE DORSOLATERAL PFC AND THE AMYGDALA ALLOWING EXTINCTION LEARNING TO QUIET THE AMYGDALA**

# **POST-TRAUMATIC STRESS DISORDER CIRCUIT**

- **SYMPTOMS SUCH AS DISTURBED SLEEP AND INCREASED VIGILANCE ARE EXPECTED IMMEDIATELY AFTER A TRAUMATIC EVENT**
- **PTSD DEVELOPES WEEKS, MONTHS AND YEARS LATER IN ABOUT 20% OF TRAUMA VICTIMS**
- **EXTINCTION CAN OCCUR VIA REPEATED EXPOSURE TO A PARTICULAR TRAUMA-RELATED MEMORY OR CUE**
- **THE FEAR RESPONSE IS REPLACED BY A NEUTRAL RESPONSE. PTSD CAN BE CONSIDERED A FAILURE OF EXTINCTION**

# **POST-TRAUMATIC STRESS DISORDER CIRCUIT**

- **EVIDENCE SUGGESTS A DYSFUNCTIONAL CIRCUIT MAKES EXTINCTION HARDER TO ACHIEVE**
- **KEY BRAIN HUBS FOR FEAR ARE THE AMYGDALA AND A GALAXY OF ADJACENT CELLS CALLED THE BED NUCLEUS OF THE STRIA TERMINALIS**
- **THESE TWO AREAS DRIVE VIRTUALLY ALL SYMPTOMS OF FEAR INCLUDING RACING HEART, INCREASED SWEATING, FREEZING AND EXAGGERATED STARTLE RESPONSE**

# **POST-TRAUMATIC STRESS DISORDER CIRCUIT**

- **IF AMYGDALA IS THE ENGINE OF FEAR, SOMETHING SHOULD BE RESPONSIBLE FOR TURNING IT OFF**
- **GREG QUIRK AT THE UNIVERSITY OF PUERTO RICO SHOWED A TINY AREA IN THE PREFRONTAL CORTEX OF RODENTS CALLED THE INFRALIMBIC REGION IS CENTRAL TO FEAR EXTINCTION**
- **ACTIVITY IN THIS AREA INCREASES DURING EXTINCTION SERVING AS A BRAKE ON THE AMYGDALA WHILE BLOCKING THE INFRALIMBIC REGION IMPAIRS EXTINCTION**

# **POST-TRAUMATIC STRESS DISORDER CIRCUIT**

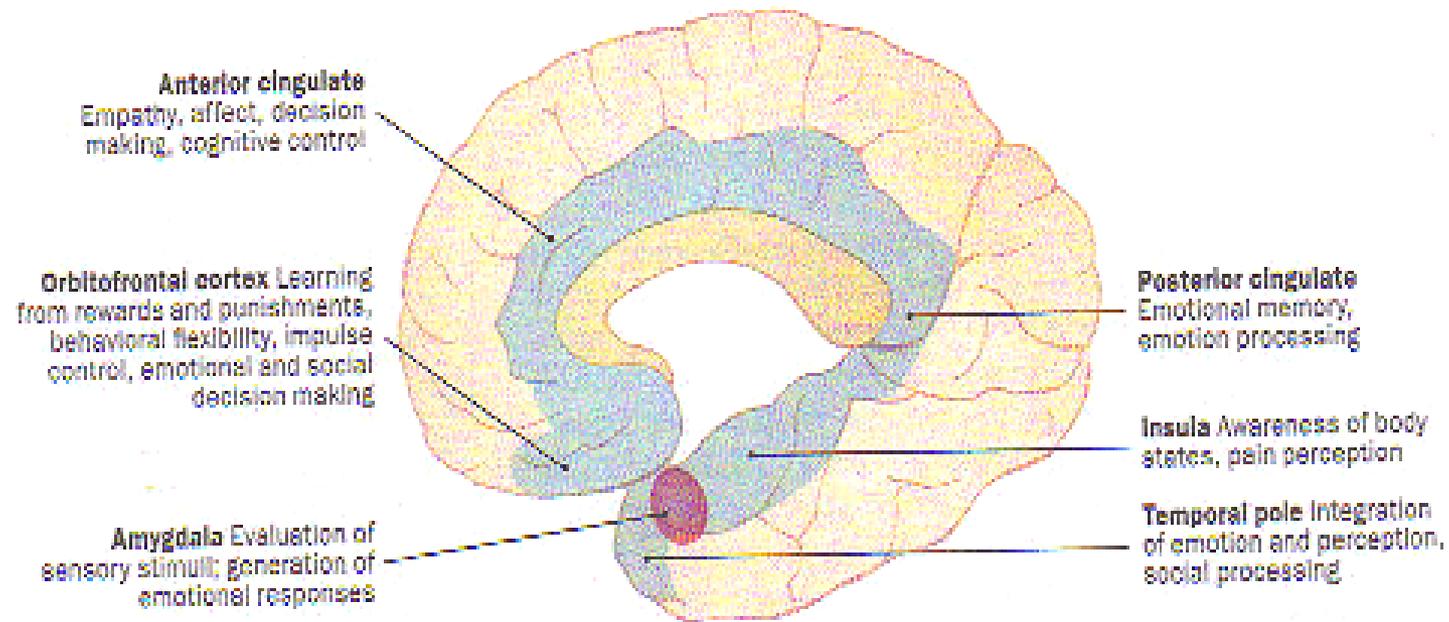
- **IN PTSD, NEUROIMAGING SHOWS REDUCED ACTIVITY IN vmPFC WHICH IS COMPARABLE TO THE RAT'S INFRALIMBIC REGION**
- **THE PATIENTS ALSO HAD SMALLER vmPFC RELATIVE TO TRAUMA –EXPOSED CONTROLS**
- **EXTINCTION INVOLVES INCREASE IN vmPFC ACTIVITY AND REDUCED FIRING OF PFC**

# **POST-TRAUMATIC STRESS DISORDER CIRCUIT**

- **IN COGNITIVE-BEHAVIORAL THERAPY IMAGING SHOWS THE IMPORTANCE OF THE HIPPOCAMPUS FOR ASSESSING CONTEXT AND THE DORSOLATERAL PFC FOR LEARNING TO TOLERATE AND OVERCOME FEAR**
- **THE DORSOLATERAL PFC DOESN'T DIRECTLY CONNECT TO THE AMYGDALA**
- **THE vmPFC IS THOUGHT TO BE THE CRITICAL LINK BETWEEN THE DORSOLATERAL PFC AND AMYGDALA ALLOWING COGNITIVE TREATMENT TO PRODUCE NEW LEARNING AND RECOVERY**

**INSEL, THOMAS. "FAULTY CIRCUITS". *SCIENTIFIC AMERICAN*. APRIL 2010, PPGS 44-51.**

# PARALIMBIC SYSTEM AND ASPD



# **PARALIMBIC SYSTEM AND ASPD**

- **PARALIMBIC SYSTEM IS A CIRCUIT OF INTERCONNECTED BRAIN REGIONS THAT MAY WELL BE THE AREA OF MALFUNCTION IN ASPD**
- **THESE INTERCONNECTED BRAIN REGIONS REGISTER FEELINGS AND OTHER SENSATIONS AND ASSIGN EMOTIONAL VALUE TO EXPERIENCES, AS WELL AS, BEING INVOLVED IN DECISION MAKING, HIGH LEVEL REASONING AND IMPULSE CONTROL**
- **AREA IS UNDERDEVELOPED IN ASPD AND DAMAGE TO THESE AREAS CAN CREATE PSYCHOPATHIC TRAITS**

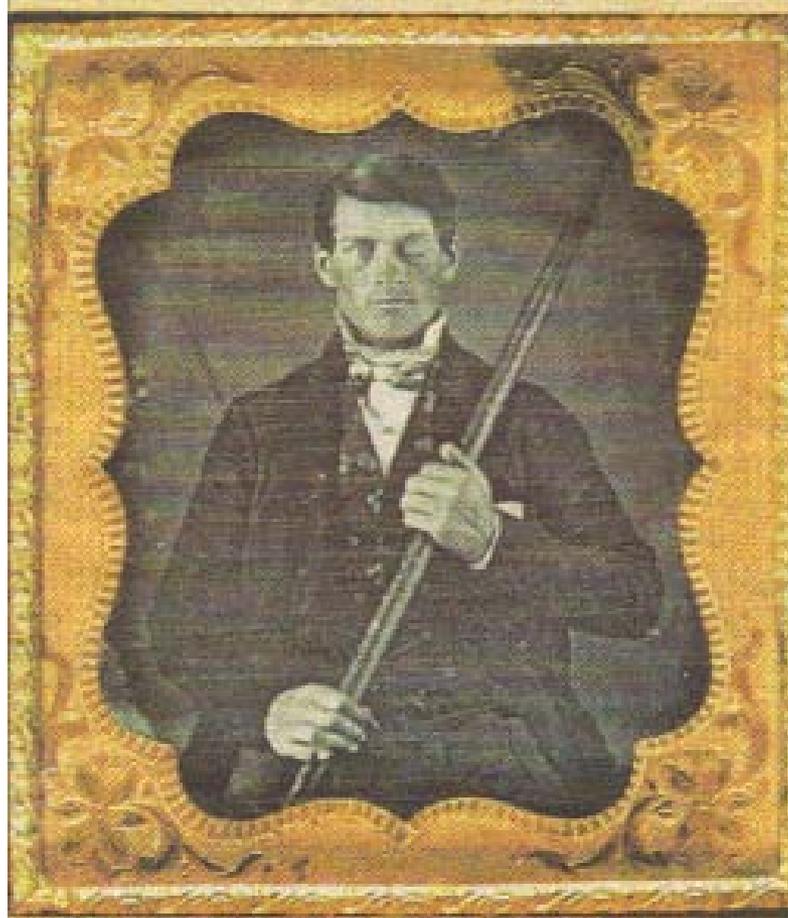
# **PARALIMBIC SYSTEM AND ASPD**

- **OFC INVOLVED IN SOPHISTICATED DECISION-MAKING TASKS THAT INVOLVE SENSITIVITY TO RISK, REWARD AND PUNISHMENT**
- **LEADS TO PROBLEMS OF IMPULSIVITY AND INSIGHT AND LASH OUT IN RESPONSE TO PERCEIVED AFFRONT**
- **THESE WERE GAGES'S PREDOMINANT SYMPTOMS ALTHOUGH HE STILL POSSESSED EMPATHY**

# **PARALIMBIC SYSTEM AND ASPD**

- **THE ANTERIOR CINGULATE REGULATES EMOTIONAL STATES AND HELPS PEOPLE CONTROL THEIR IMPULSES AND MONITOR THEIR BEHAVIOR FOR MISTAKES**
- **THE INSULA PLAYS A KEY ROLE IN THE RECOGNITION OF VIOLATION OF SOCIAL NORMS, AS WELL AS, THE EXPERIENCING OF ANGER, FEAR, EMPATHY AND DISGUST**
- **INSULA ALSO INVOLVED IN PAIN PERCEPTION AND PSYCHOPATHS ARE STRIKINGLY UNFAZED BY THREAT OF PAIN**

# PHINEAS GAGE



# **PHINEAS GAGE**

- **43 INCHES LONG, 1.25 INCHES IN DIAMETER AND WEIGHING 13.25 POUNDS THE TAMPING IRON PENETRATED THE LEFT CHEEK AND EXITING THROUGH THE SKULL**
- **LOST A PART OF HIS BRAIN CALLED THE VENTROMEDIAL PREFRONTAL CORTEX (VMPFC) AN AREA STRUCTURALLY SIMILAR TO THE ORBITOFRONTAL CORTEX (OFC)**

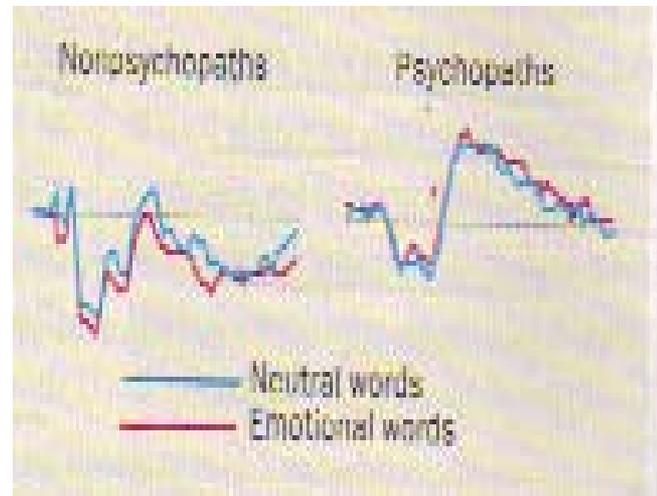
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# **PARALIMBIC SYSTEM AND ASPD**

- **EMPATHY INVOLVES MANY AREAS OF THE BRAIN BUT THE AMYGDALA SEEMS TO BE A CENTRAL PLAYER AS IT GENERATES EMOTIONS SUCH AS FEAR-CREATES FEARLESSNESS**
- **ASPD NOTED FOR FEARLESSNESS-WHEN CONFRONTED WITH AN ATTACKER THEY DO NOT BLINK**
- **THEIR EEG READINGS ARE CONSISTENT WHEN SHOWN WORDS LIKE “BLOOD” AND “HOUSE” ( A NEUTRAL WORD), THE PATTERNS ARE ALSO DIFFERENT THAN CONTROLS**

# PARALIMBIC SYSTEM AND ASPD



# **PARALIMBIC SYSTEM AND ASPD**

- **EMPATHY INVOLVES OTHER AREAS OF BRAIN SUCH AS**
  - **ORBITOFRONTAL CORTEX**
    - **EMOTIONAL AND SOCIAL DECISION MAKING**
  - **ANTERIOR CINGULATE**
    - **AFFECT, DECISION MAKING AND COGNITIVE CONTROL**
  - **DORSOLATERAL PREFRONTAL CORTEX**
    - **COGNITIVE FLEXIBILITY**

# **PARALIMBIC SYSTEM AND ASPD**

- **THE ANTERIOR CINGULATE REGULATES EMOTIONAL STATES AND HELPS PEOPLE CONTROL THEIR IMPULSES AND MONITOR THEIR BEHAVIOR FOR MISTAKES**
- **THE INSULA PLAYS A KEY ROLE IN THE RECOGNITION OF VIOLATION OF SOCIAL NORMS, AS WELL AS, THE EXPERIENCING OF ANGER, FEAR, EMPATHY AND DISGUST**
- **INSULA ALSO INVOLVED IN PAIN PERCEPTION AND PSYCHOPATHS ARE STRIKINGLY UNFAZED BY THREAT OF PAIN**

# **PARALIMBIC SYSTEM AND ASPD**

- **fMRI IMAGES OF BRAINS (KIEHL) SHOW PRONOUNCED THINNING OF PARALIMBIC TISSUE INDICATING THE AREA IS UNDERDEVELOPED**

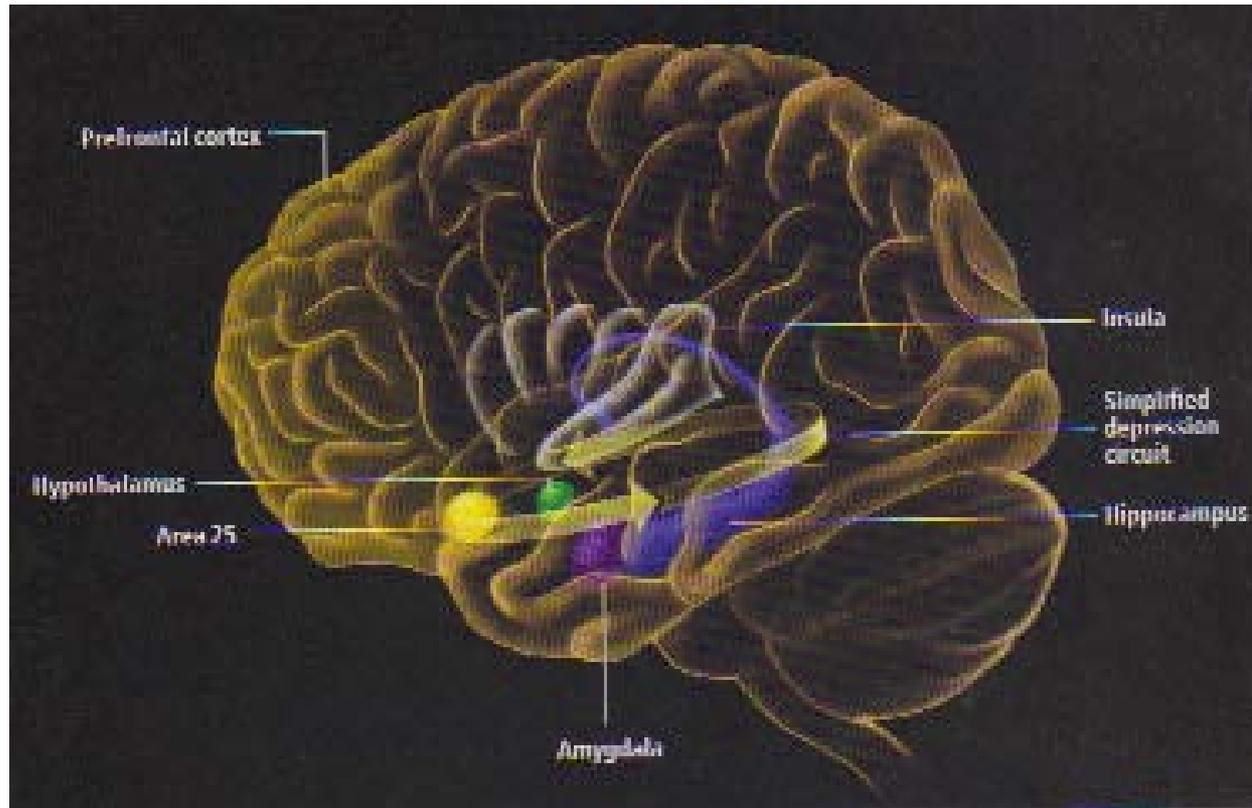
# **PARALIMBIC SYSTEM AND ASPD**

- **IS ASPD MADE OR BORN?**
  - **COMBINATION OF NATURE AND NURTURE- GENES AND ENVIRONMENT**
    - **SOME ARE SCARED BY EARLY ENVIRONMENT OTHERS ARE “BLACK SHEEP” OF STABLE FAMILIES**
- **ARE THEY TREATABLE?**
  - **ASPD IS A DISORDER OF RANGE, THE FAR END IS THE PSYCHOPATH WHO IS DIFFICULT, IF NOT IMPOSSIBLE, TO TREAT WITH TODAY’S TECHNOLOGY.**

# **PARALIMBIC SYSTEM AND ASPD**

- **ONE WAY OF CONSIDERING TREATMENT IS TO THINK OF DEVELOPMENT AS OCCURRING EASIEST DURING CERTAIN PERIODS OF LIFE OFTEN CALLED “CRITICAL PERIODS”**
  - **CHILDHOOD AND EARLY ADOLESCENCE MAY BE A WINDOW FOR DEVELOPING SOCIAL AND COGNITIVE SKILLS WE CALL “CONSCIENCE”**

# DEPRESSION CIRCUIT



# **DEPRESSION CIRCUIT**

- **BRODMANN AREA 25 ACTS AS A HUB OF THE DEPRESSION CIRCUIT**
- **AREA 25 CONNECTS DIRECTLY TO THE AMYGDALA WHICH MEDIATES ANXIETY AND FEAR, AND THE HYPOTHALAMUS INVOLVED IN STRESS REPOSSES**
- **THESE REGIONS EXCHANGE SIGNALS WITH THE HIPPOCAMPUS, A CENTER OF MEMORY PROCESSING, AND THE INSULA WHERE SENSORY PERCEPTION AND EMOTIONS ARE PROCESSED**
- **A SMALLER AREA 25 IS SUSPECTED OF CREATING A HIGHER RISK OF DEPRESSION IN PEOPLE WITH A GENE VARIANT THAT INHIBITS SEROTONIN PROCESSING**

# DEPRESSION CIRCUIT

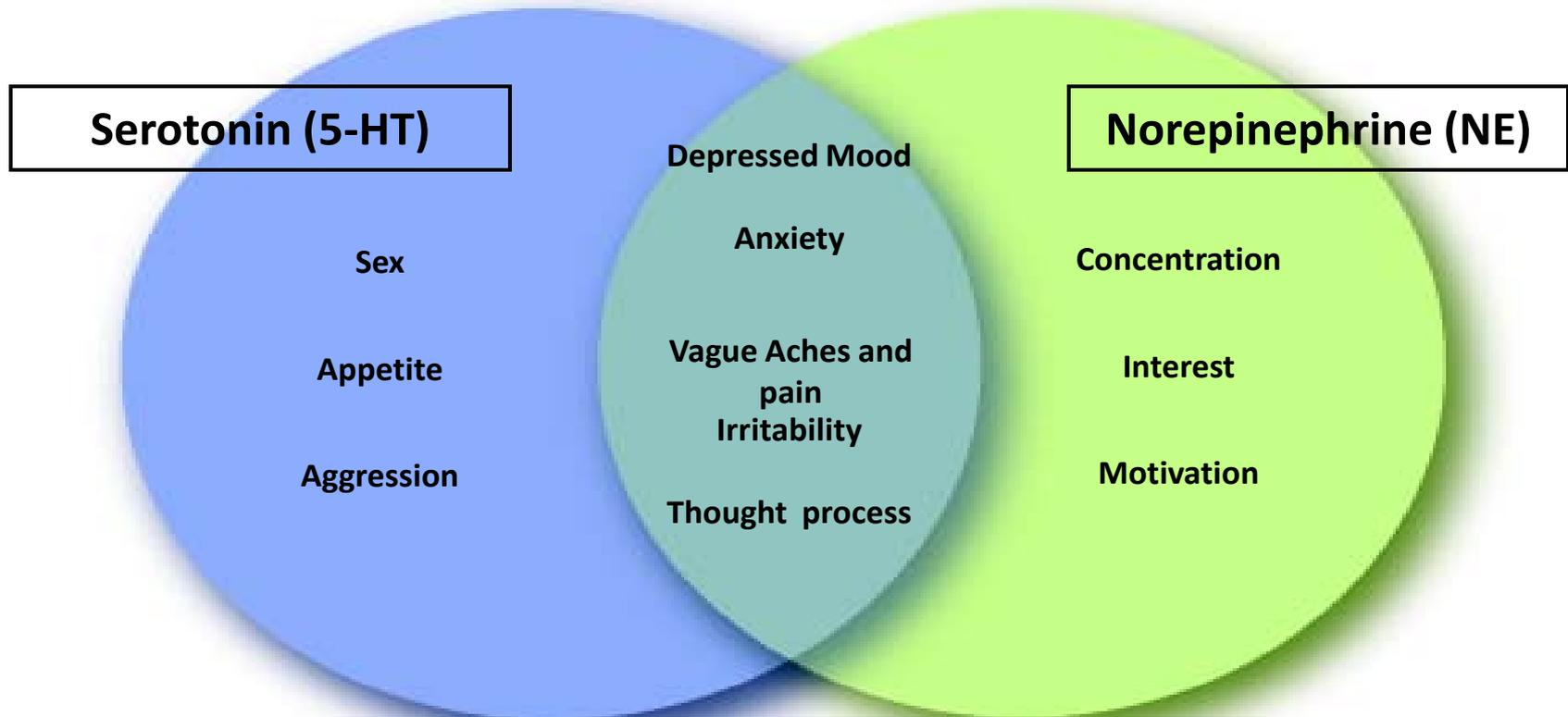
- HELEN MAYBERG AT EMORY HAS SHOWN AREA 25 IS OVERLY ACTIVE IN DEPRESSED PATIENTS AND SYMPTOM IMPROVEMENT IS CORRELATED WITH REDUCED ACTIVITY
- AREA 25 IS EXCEPTIONALLY RICH IN SEROTONIN TRANSPORTERS AND THOSE WITH A SHORT VARIANT OF THE SEOTONIN TRANSPORTER GENE HAVE A RELATIVE “UNCOUPLING” WITH SUBCORTICAL AREAS AND ALSO CONNECTION WITH FRONTAL CORTEX THATDISTURBS INSIGHT AND SELF-ESTEEM. CAN LEAD TO DISTORTED ASSESSMENT OF THE INTERNAL AND EXTERNAL WORLD

# DEPRESSION CIRCUIT

- **“UNCOUPLING” CAUSES DISRUPTED CONNECTIONS WITH...**
  - **HYPOTHALAMUS**
    - *CHANGES IN APPETITE*
    - *CHANGES IN SLEEP*
    - *CHANGES IN ENERGY*
  - **AMYGDALA AND INSULA**
    - *ANXIETY*
    - *MOOD CHANGES*
  - **HIPPOCAMPUS**
    - *MEMORY PROCESSING*
    - *ATTENTION*

# There are at least two sides to the neurotransmitter story

Functional domains of Serotonin and Norepinephrine<sup>1-4</sup>



- Both serotonin and norepinephrine mediate a broad spectrum of depressive symptoms

# **SUFFERING AND MISERY**

- **Let's start with a real or perceived threat**
  - **The amygdala reacts sending signals to:**
    - **Thalamus**
      - **To brain stem to increase norepinephrine (NE) throughout the brain**
    - **Sympathetic Nervous System (SNS)**
      - **Sends signals to major organs and muscle groups**
        - » **“Flight or Fight”**
    - **Hypothalamus**
      - **To pituitary releasing stress hormones**
        - » **Epinephrine (increases HR and dilates pupils)**
        - » **Cortisol**

# **SUFFERING AND MISERY**

- **Cortisol**
  - **Suppresses immune system to reduce inflammation**
  - **Continues to stimulate the amygdala**
  - **Suppresses hippocampal activity which normally inhibits amygdala leading to more cortisol**
  - **Remember amygdala hardwired to focus on negative**
  - **PFC is overridden pushing its appraisal in a negative direction**

# **MENTAL CONSEQUENCES OF SNS/HPA ACTIVATION**

- **ANXIETY**

- **If amygdala gets neurosensitized causes**

- **Rapid arousal of “state” anxiety (based on specific situations)**
    - **Helps form implicit memories and shades these memories with fear thus intensifying “trait” anxiety (free floating)**
    - **With frequent SNS/HPAA activation hippocampus wears down impacting explicit memories (clear record of what actually happened)**
      - **Cortisol inhibits new neuronal growth and weakens existing synaptic connections in hippocampus**
      - **May help explain dissociation**
        - » **“Know something happened, don't exactly know what happened but feel really upset”**

# **MENTAL CONSEQUENCES OF SNS/HPA ACTIVATION**

- **DEPRESSION**

- When norepinephrine is reduced may feel flat or even apathetic with poor concentration
- Over time glucocorticoids (cortisol, etc) reduce dopamine causing loss of feeling of well-being and enjoyment of life
- Constant stress reduces serotonin levels
  - The most important neurotransmitter for maintaining good mood state

# **MENTAL CONSEQUENCES OF SNS/HPA ACTIVATION**

- **Psychotherapy**
- **Pharmacotherapy**
- **Activation of parasympathetic nervous system**
  - **Responsible for steady-state**
  - **Produces feelings of relaxation**
    - **Touching lips**
    - **Breathing**
    - **Forms of meditation and relaxation**

# MEMORY

- **Explicit and implicit memories when made only key features are stored**
- **When brain retrieves it is not like a computer that pulls up the whole file**
- **Brain rebuilds memory from key features**
  - **Simulation**
- **Each recollection is shaded by the emotional state especially if unpleasant or pleasant**

# MEMORY

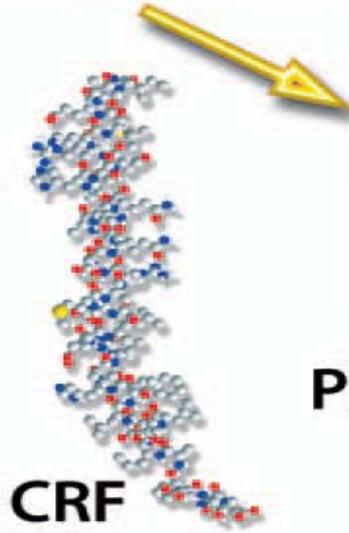
- Amygdala and hippocampus will associate them with neural patterns
- **When recollection take place it is now with these associations**
  - **Example-If increasingly associate negative feeling states with memory it will become more negative. On the other hand, if add positive meaning and feelings to the memory you start to build a more positive view (positive feelings also increase immune and cardiovascular functioning and lift mood)**

# **HYPOTHALAMIC-PITUITARY-ADRENAL AXIS (HPA)**

- **HPA is an integral part of the stress response, as is the sympathetic nervous system, both also affect the immune system**
- **Studies of early life trauma**
  - **Some studies show *blunted HPA response* in adults and others show *hyperresponsive HPA***
  - **Reduction in hippocampal volume**
  - **Increase in autoimmune disorders**

# Stress

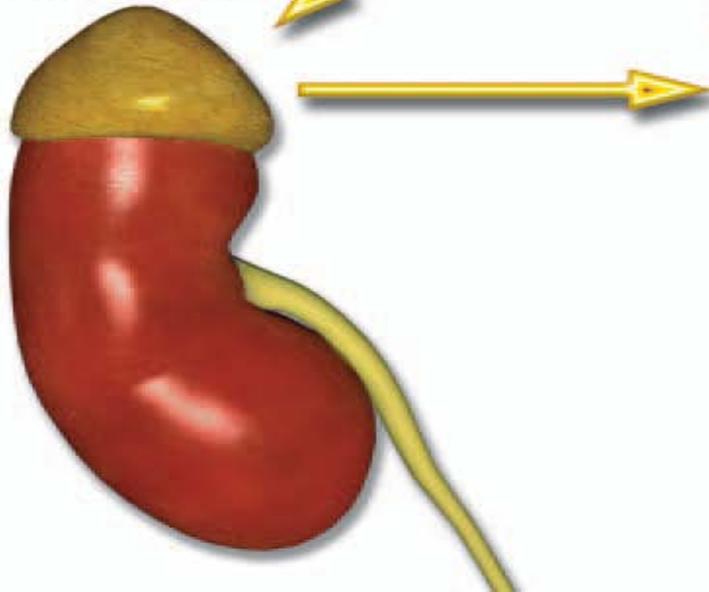
Hypothalamus:  
Paraventricular  
Nucleus



Pituitary

ACTH

Adrenal



Cortisol

# **AUTONOMIC NERVOUS SYSTEM (ANS)**

- **Alterations in cardiovascular response with history of early life trauma**
  - **Heart rate and blood pressure elevations**
    - **Stress excites the locus coeruleus-norepinephrine system**
  - **Greater incidence of ischemic heart disease (IHD)**
    - **Depression also associated with increase in IHD**
      - **Increased risk of depression in early life trauma survivors**
  - **General increased risk of heart disease**

# **OTHER MANIFESTATIONS**

- **Increased rates of obesity and eating disorders**
- **Increase in many psychiatric disorders**
- **Low cognitive functioning and/or poor attention**
  - **Neurodevelopmental possibilities**

# **LEFT AND RIGHT HEMISPHERE**

- **Right Hemisphere-Parallel Processor**
- **Left Hemisphere-Serial Processor**
- **Communicate through the Corpus Collosum**
  - 300 million axonal fibers
- **Each hemisphere thinks differently and care about different things**

# **RIGHT HEMISPHERE**

- **The Present Moment-Right here and now**
- **Thinks in pictures and symbols**
- **Receives sensory information that allows us to understand what the moment feels like, smells like and tastes like**
  - **Sensory collage**
- **Connects to the energy all around us**
- **We are energy beings connected to everything through the consciousness of our right hemisphere**

# **LEFT HEMISPHERE**

- **Linear and methodical**
- **All about the past and the future**
- **Takes the collage of the present moment and categorizes and organizes the informational details**
- **It then associates this information with what we have learned from the past and projects it into the future**

# LEFT HEMISPHERE

- **Thinks in language**
- **It is the ongoing chatter in the brain**
- **It is calculating intelligence (survival and gain)**
- **It says, “I am”**
  - **This separates us from everything else**
- **The “Experiencer”**
  - **Ego**
  - **Animal brain heritage**

# **LEFT/RIGHT BRAIN**

- **If disconnected from the brain chatter that connects us to the outer world the mind is silent**
- **Lose the complications of the past and future and become overwhelmed by the peacefulness of the moment**
- **The more time we spend in the inner circuitry of our right hemisphere the more peace we project into the world**

# **SPLIT BRAIN RESEARCH**

- ✘ Right hemisphere (RH) processes only what it receives and nothing more**
- ✘ Left hemisphere (LH) appears to make elaborations, associations and searches for logical patterns even when none are present**
- ✘ RH retains veridical (actual; genuine) representations of each to-be-remembered item and tends to accurately recognize previously viewed items and reject new items even when they are similar (Turk et al, 2003)**

# **SPLIT BRAIN RESEARCH**

- ✘ LH tends to elaborate and make inferences about the material presented often at the expense of veracity (Metcalf, 1995, Phelps & Gazzaniga, 1992)**
- ✘ LH also attempts to assign a coherent explanation to events or behavior even when none is present (Wolford, 2000)**
  - † Described as the LEFT HEMISPHERE INTERPRETER  
Turk et al, 20030**

# **SPLIT BRAIN RESEARCH**

- ✘ Interpretive function of the LH takes available information from the distributed self-processing networks and creates a unified sense of self from the input**
  - + I AM**
  - + Dualistic EGO**
- ✘ Interpretive function tries to make sense out of incomplete or ambiguous data**

# **SPLIT BRAIN RESEARCH**

- ✘ The LEFT HEMISPHERE INTERPRETER seems to be the link between trying to make sense of the world and the perception of self in the LH**
- ✘ This might explain why everyone's reality and perception of the world are different and an illusion as described by spiritual traditions such as Buddhism and Hinduism**

# **LEFT/RIGHT BRAIN**

- **LEFT HEMISPHERE**
  - **CONSCIOUS**
  - **SERIAL**
  - **INFORMATION PROCESSING**
- **RIGHT HEMISPHERE**
  - **UNCONSCIOUS**
  - **NONVERBAL**
  - **EMOTIONAL PROCESSING**

# **RIGHT HEMISPHERE**

- **EARLY DEVELOPMENTAL UNCONSCIOUS**
- **EMOTIONAL “SELF”**
- **80-90% IS UNCONSCIOUS**
- **THE ABOVE DRIVES OR MOTIVATES HUMAN EMOTION**
- **HUMAN EMOTION IS THE DRIVING FORCE BEHIND COGNITION AND BEHAVIOR**
- **EMOTION IS MEDIUM IN WHICH PRIMARY INTERPERSONAL INFORMATION IS TRANSMITTED**

# **RIGHT HEMISPHERE (RH)**

- **RECOGNITION AND EXPRESSION OF EMOTION**
- **NONVERBAL EMOTIONAL EXPRESSION**
- **RH TO RH AFFECTIVE COMMUNICATION EQUALS THE RELATIONAL UNCONSCIOUS**
- **UNCONSCIOUS RH IMPLICIT SELF CONTINUOUSLY APPRAISES LIFE EXPERIENCES AND RESPONDS ACCORDING TO ITS SCHEME OF INTERPRETATION**

# **RIGHT HEMISPHERE (RH)**

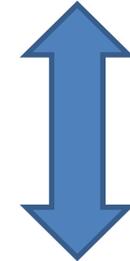
- **ONE UNCONSCIOUS MIND COMMUNICATES WITH ANOTHER UNCONSCIOUS MIND**
- **RH RESPONDS QUICKLY TO ALL STIMULI**
- **IMPLICIT LEVEL OF THE THERAPEUTIC ALLIANCE (BENEATH THE EXPLICIT COGNITIONS AND LANGUAGE) ARE THE CORE OF THE CHANGE MECHANISM AT THE UNCONSCIOUS LEVEL**

# RIGHT HEMISPHERE (RH)

LEFT HEMISPHERE  
LANGUAGE



RIGHT HEMISPHERE  
IMAGES



LIMBIC SYSTEM

MOTIVATION & EMOTION



BRAIN STEM

ANS, AROUSAL & PAIN

# **RIGHT HEMISPHERE (RH)**

- **INVOLVES CO-CREATION OF AN INTERSUBJECTIVE CONTEXT THAT FACILITATES THE PROCESS OF CHANGE (ATTACHMENT COMMUNICATION)**
- **ATTACHMENT COMMUNICATION REPRESENTS RH TO RH TRANSACTION THAT FACILITATE THE EXPERIENCE DEPENDENT MATURATION OF RH**

# **RIGHT HEMISPHERE (RH)**

- **EMOTIONAL AVAILABILITY OF CAREGIVER IN INTIMACY SEEMS TO BE THE CENTRAL GROWTH PROMOTING FACTOR IN EARLY REARING EXPERIENCE**
- **CAREGIVER MAXIMIZES POSITIVE AFFECT AND MINIMIZES NEGATIVE AFFECT**
- **PROMOTES INCREASED TOLERANCE FOR POSITIVE AND NEGATIVE AFFECT (AFFECTIVE RANGE)**

# **RIGHT HEMISPHERE (RH)**

- **THE BROADER THE RANGE OF EMOTIONS THAT A CHILD EXPERIENCES THE BROADER WILL BE THE EMOTIONAL RANGE OF THE SELF THAT DEVELOPES**
- **THERAPEUTIC ALLIANCE**
  - **THERAPIST'S FACILITATING BEHAVIORS COMBINE WITH THE PATIENTS CAPACITY FOR ATTACHMENT TO PERMIT DEVELOPMENT OF ALLIANCE (PRIMARY COMPONENT OF EMOTIONAL BOND)**

# **RIGHT HEMISPHERE (RH)**

- **THERAPEUTIC ALLIANCE (CONTINUED)**
  - **KEY IS HOW TO BE SUBJECTIVELY WITH PATIENT ESPECIALLY DURING AFFECTIVELY STRESSFULL MOMENTS**
    - **UNCONSCIOUS INTERSUBJECTIVE PROCESSES INCLUDE EMPATHY, IDENTIFICATION WITH OTHERS AND SELF-AWARENESS**
  - **FACIAL EXPRESSIONS CAN BE APPRAISED BY THE RH WITHIN 30 MILLISECONDS**
    - **MAY TAKE HOURS TO DAYS TO GET INTENSE REACTION BACK TO BASE LINE**

# **RIGHT HEMISPHERE (RH)**

- **MUST BE ATTENTIVE TO LH PATIENT VERBALIZATIONS IN ORDER TO OBJECTIVELY DIAGNOSE AND UNDERSTAND PATIENTS DYSREGULATED SYMPTOMS**
- **BUT ALSO ATTENTIVE INTERSUBJECTIVELY TO RELATIONAL TRANSACTIONS (REFLECT EMOTIONS SUCH AS APPROVAL/DISAPPROVAL, SUPPORT, HUMOR AND FEAR)**
  - **FACIAL EXPRESSIONS**
  - **BODY POSTURE**
  - **TONE AND TEMPO OF VOICE**

# **RIGHT HEMISPHERE (RH)**

- **RIGHT SIDE OF FACE (LH)-SOCIALY CONSCIOUS CONTENT, SOCIALY APPROPRIATE CLUES**
- **LEFT SIDE OF FACE (RH)-HIDDEN PERSONALIZED FEELINGS, IMPLICIT UNCONSCIOUS CONTENT**
- **IN HEIGHTENED AFFECTIVE MOMENT THE EMPATHIC THERAPIST'S RH CAN REGULATE PATIENTS DYSREGULATED RH**

# **RIGHT HEMISPHERE (RH)**

- **CARL ROGERS (1986)**

**“AS A THERAPIST, I FIND THAT WHEN I AM CLOSEST TO MY INNER, INSTINCTIVE SELF, WHEN I AM SOMEHOW IN TOUCH WITH THE UNKNOWN IN ME, WHEN PERHAPS I AM IN A SLIGHTLY ALTERED STATE OF CONSCIOUSNESS IN THE RELATIONSHIP, THEN WHATEVER I DO SEEMS FULL OF HEALING.”**

# ***BRAIN PHYSIOLOGY***

- **LEFT TO RIGHT HEMISPHERE**
- **AT LOW LEVELS OF CONSCIOUSNESS**
  - **FAST FLOW TO AMYGDALA AND EMOTIONAL BRAIN**
- **AS LEVELS OF CONSCIOUSNESS INCREASES**
  - **FAST FLOW TO PREFRONTAL CORTEX**
  - **DEVELOPMENT OF ETHERIC BRAIN (ENERGY BRAIN) AND “THIRD EYE”**
  - **KUNDALINI ENERGY**

# ***PREFRONTAL-ANTERIOR CINGULATE- BASAL GANGLIA-THALAMUS-PREFRONTAL CIRCUIT***

- THIS CIRCUIT CONTROLS:
  - *CONSCIOUSNESS*
  - *CLARITY OF MIND*
  - *REALITY FORMATION*
  - *ERROR DETECTION*
  - *EMPATHY*
  - *COMPASSION*
  - *EMOTIONAL BALANCE*
  - *SUPPRESSION OF FEAR AND ANGER*

NEWBERG, ANDREW. *HOW GOD CHANGES YOUR BRAIN.*

# ***BRAIN PHYSIOLOGY***

- ***POSITIVE EFFECTS OF MEDITATION AND CONTEMPLATION***
  - ***STIMULATES ANTERIOR CINGULATE GYRUS***
    - ***COMPASSION***
    - ***MAINTAINS BALANCE BETWEEN THE FRONTAL LOBES (INITIATE THOUGHTS AND BEHAVIORS) AND LIMBIC SYSTEM (PROCESSES FEELINGS AND EMOTIONS)***
    - ***ANTERIOR CINGULATE***
      - ***EMOTIONAL REGULATION***
      - ***LEARNING***
      - ***MEMORY***
      - ***PLAYS ROLE IN LOWERING ANXIETY AND IRRITABILITY***
      - ***COUNTERS DEPRESSION***
      - ***ENHANCES SOCIAL AWARENESS***

# ***BRAIN PHYSIOLOGY***

- **SPIRITUAL VALUES CAUSE INCREASE IN BLOOD SUPPLY TO FRONTAL CORTEX AND ANTERIOR CINGULATE AND REDUCED BLOOD FLOW TO LIMBIC AREAS (AMYGDALA)**
- **ANGER CAUSES JUST THE OPPOSITE REACTION**
- **MEDITATION/CONTEMPLATION ENHANCES ACTIVITY OF THE *PREFRONTAL-ANTERIOR CINGULATE-BASAL GANGLIA-THALAMUS-PREFRONTAL CIRCUIT***

# ***BRAIN PHYSIOLOGY***

- **FRONTAL LOBES**
  - ***SELECTIVE ATTENTION***
  - ***EXPECTATION***
  - ***OPTIMISM***
  - ***INTENTION***
- ***KEYS TO BELIEF THAT ONE'S ACTIONS CAN MAKE A SPIRITUAL DIFFERENCE IN SELF AND THE WORLD***

# SEEKING SYSTEM

- **IN 1954 JAMES OLDS AND PETER MILNER OF MCGILL UNIVERSITY DISCOVERED WHAT THEY REFERRED TO AS THE REWARD, PLEASURE OR REINFORCEMENT SYSTEM**
- **WHAT THEY ACTUALLY DISCOVERED WAS A SYSTEM THAT IS INTEGRATED THROUGHOUT THE BRAIN AND MIGHT BE BEST DESCRIBED AS THE SEEKING SYSTEM**

# SEEKING SYSTEM

**“THESE CIRCUITS APPEAR TO BE MAJOR CONTRIBUTORS TO OUR FEELINGS OF ENGAGEMENT AND EXCITEMENT AS WE SEEK THE MATERIAL RESOURCES NEEDED FOR BODILY SURVIVAL, AND ALSO WHEN WE PURSUE THE COGNITIVE INTERESTS THAT BRING POSITIVE EXISTENTIAL MEANING INTO OUR LIVES.”**

# SEEKING SYSTEM

**“HIGHER AREAS OF THE MOTOR CORTEX ARE ALSO ENERGIZED INTO ACTION BY THE PRESENCE OF DA. WITHOUT THE SYNAPTIC ‘ENERGY’ OF DA, THESE POTENTIALS REMAIN DORMANT AND STILL. WITHOUT DA, HUMAN ASPIRATIONS REMAIN FROZEN, AS IT WERE, IN AN ENDLESS WINTER OF DISCONTENT.”**

**PANKSEEP, J. *AFFECTIVE NEUROSCIENCE*. OXFORD UNIVERSITY PRESS. NEW YORK, 1998, PG 144.**

# SEEKING SYSTEM

- **WITHOUT DA ONLY THE STRONGEST EMOTIONAL MESSAGES INSTIGATE BEHAVIOR**
- **WHEN DA SYNAPSES ARE ACTIVE IN ABUNDANCE A PERSON FEELS LIKE THEY CAN DO ANYTHING**
- **IT IS NO MYSTERY WHY COCAINE, METHAMPHETAMINE AND OTHER DRUGS ARE SO REINFORCEING**

# SEEKING SYSTEM

- **DA EXCESS**
  - **MAY SEEK SPIRITUAL HEIGHTS**
  - **APPEAR MANIC**
  - **OUR IMAGINATION OUTSTRIPS THE CONSTRAINTS OF REALITY**
  - **BEGIN TO SEE CAUSALITY WHERE THERE IS ONLY CORRELATION**

# SEEKING SYSTEM

- **DA EXCESS (CONTINUED)**
  - **HIGH ANTICIPATION, INTENSE INTEREST AND INSATIABLE CURIOSITY**
  - **MOST ARRESTING PART IS THE HUNT, NOT THE CAPTURE**
  - **DA IS RELEASED FROM THE VENTRAL STRIATUM (NUCLEUS ACCUMBENS) OF RATS QUITE VIGOROUSLY DURING THE ANTICIPATION PHASE BUT NOT DURING THE CONSUMATORY PHASE**

# SEEKING SYSTEM

- **CRITICAL CIRCUITS**
  - **MEDIAL FOREBRAIN BUNDLE OF THE LATERAL HYPOTHALAMUS (LH)**
  - **EXTENDED LATERAL HYPOTHALAMIC CORRIDOR (LH)**
    - **RESPONDS TO HOMEOSTATIC IMBALANCES (BODY NEED STATES)**
    - **ENVIRONMENTAL INCENTIVES**
  - **LH CONTINUUM RUNNING FROM VTA TO NAc**
    - **WHEN EVOKED GET STRONGEST AND MOST ENERGIZED EXPLORATION AND SEARCH BEHAVIORS**

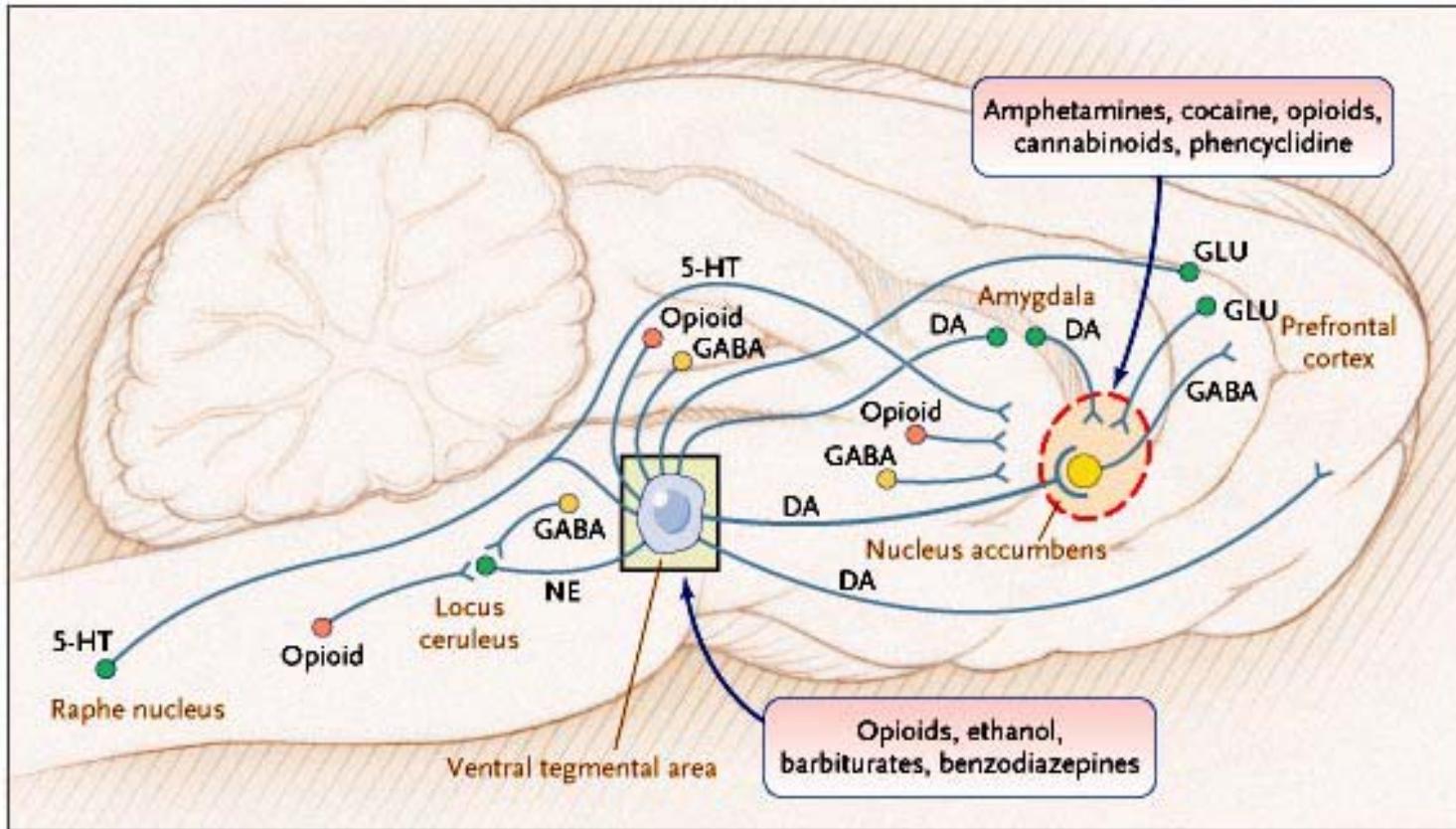
# SEEKING SYSTEM

- **CRITICAL CIRCUITS (CONTINUED)**
  - **BASIC IMPULSE TO SEARCH, INVESTIGATE AND MAKE SENSE OF ENVIRONMENT EMERGES FROM THE CIRCUITS THAT COURSE THRU THE LH**
  - **NEUROEMOTIONAL SYSTEM THAT DRIVES AND ENERGIZES MANY MENTAL COMPLEXITIES THAT HUMANS EXPERIENCE SUCH AS PERSISTENT FEELINGS OF INTEREST, CURIOSITY, SENSATION SEEKING AND IN THE PRESENCE OF A SUFFICIENTLY COMPLEX CORTEX-THE SEARCH FOR HIGHER MEANING**

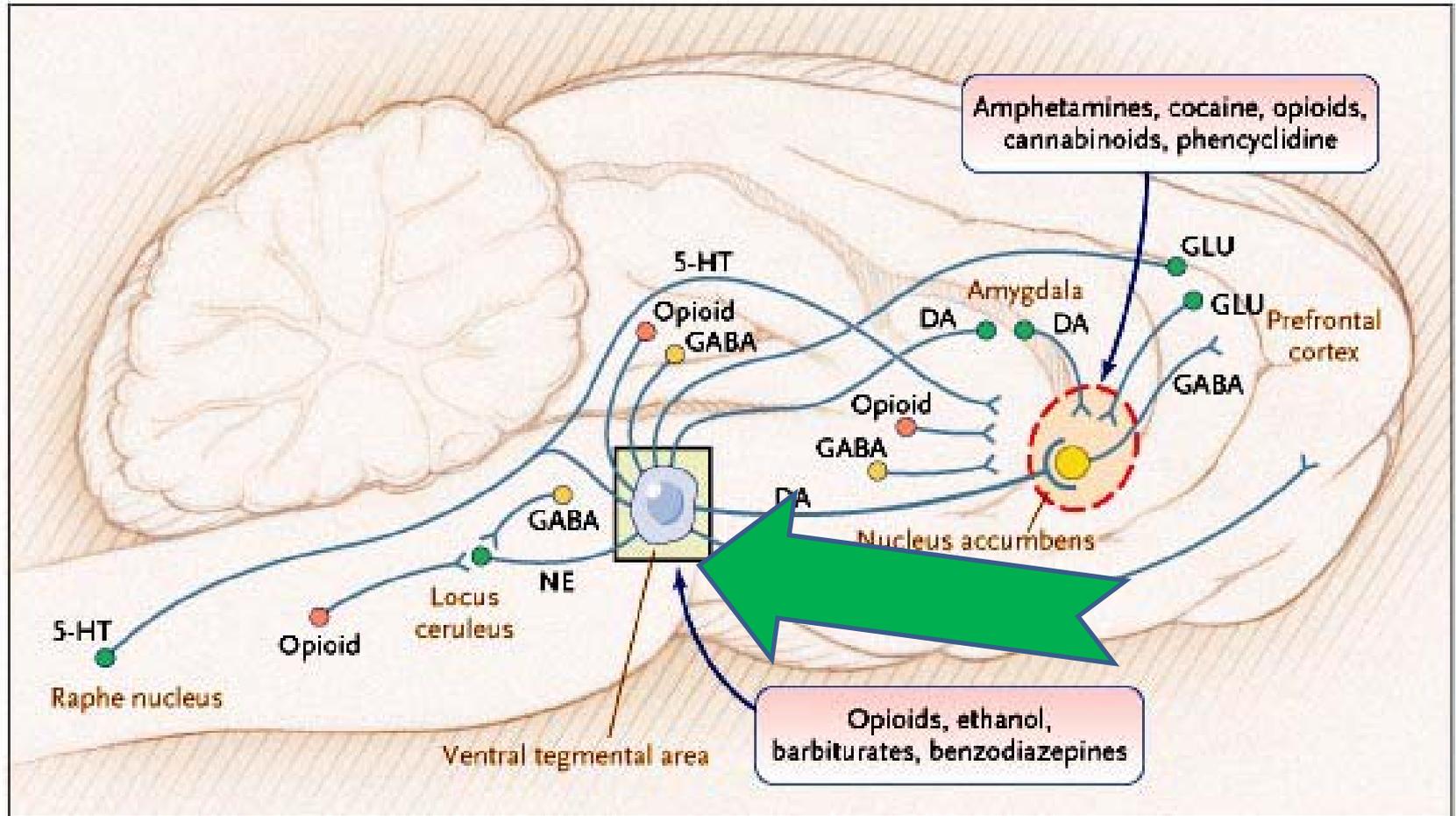
# SEEKING SYSTEM

- **SENSITIZED BY**
  - **REGULATORY IMBALANCES TO YIELD GENERAL AROUSAL AND PERSISTENT FORWARD LOCOMOTION**
  - **EXTERNAL STIMULI THAT CAN HAVE EITHER STRONG OR WEAK INTERACTIONS WITH THIS EMOTIONAL SYSTEM**
  - **HELPS MEDIATE APPETITIVE LEARNING SO THAT ANIMALS WILL BECOME EAGER AND EXHIBIT EXPECTANCIES IN RESPONSE TO PREVIOUSLY AROUSING CUES (REINFORCEMENT)**

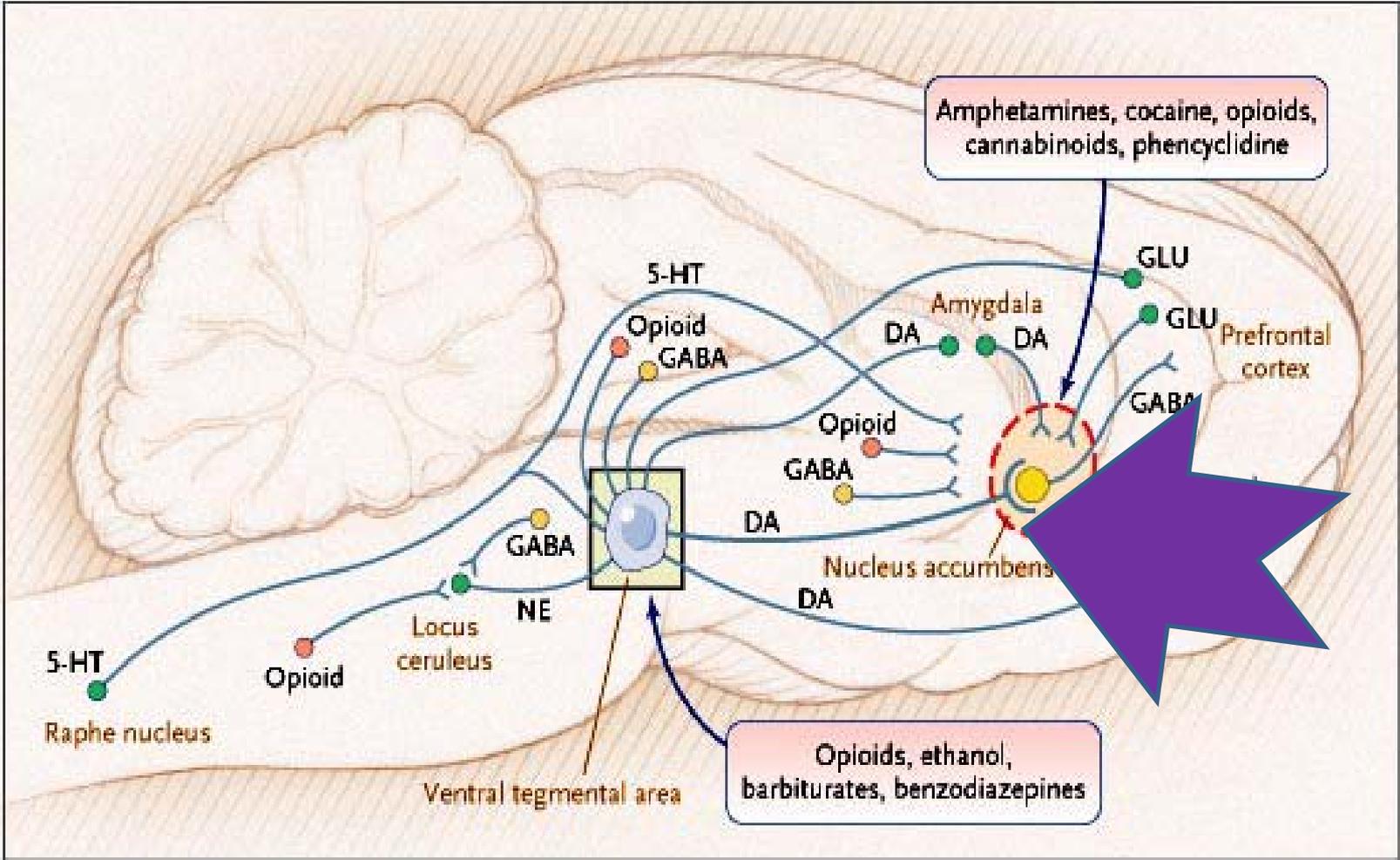
# WHO'S IN CHARGE HERE?



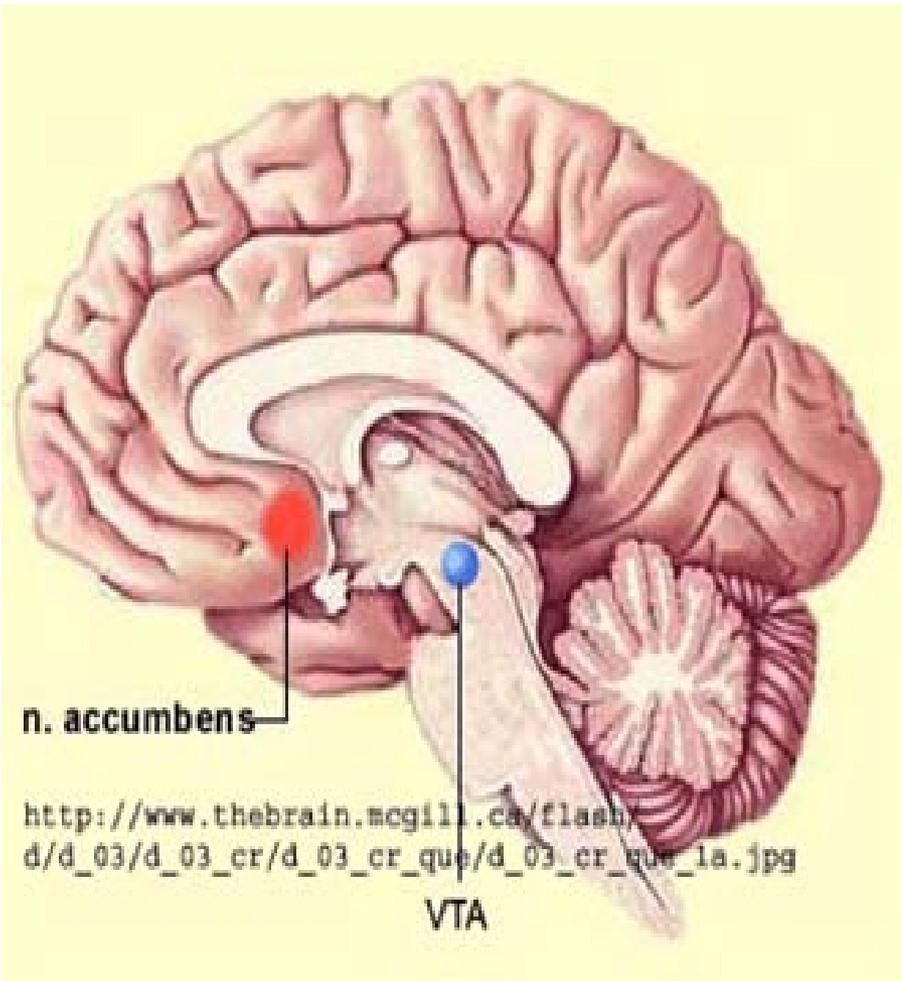
# VENTRAL TEGMENTAL AREA (“GAS TANK”) SUPPLIES DOPAMINE TO THE NUCLEUS ACCUMBENS



# NUCLEUS ACCUMBENS-GO!

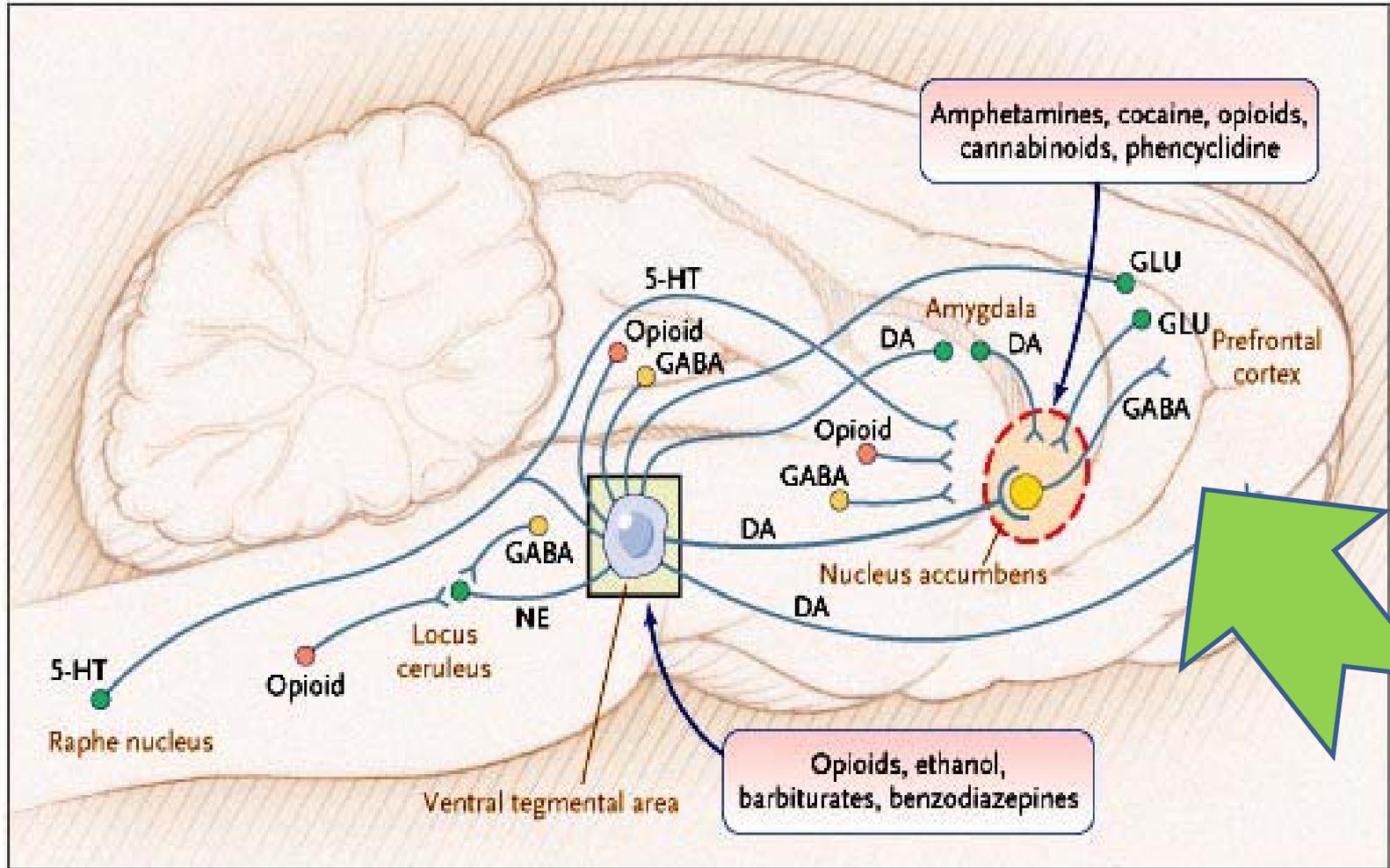


# NUCLEUS ACCUMBENS-PLEASURE CENTER

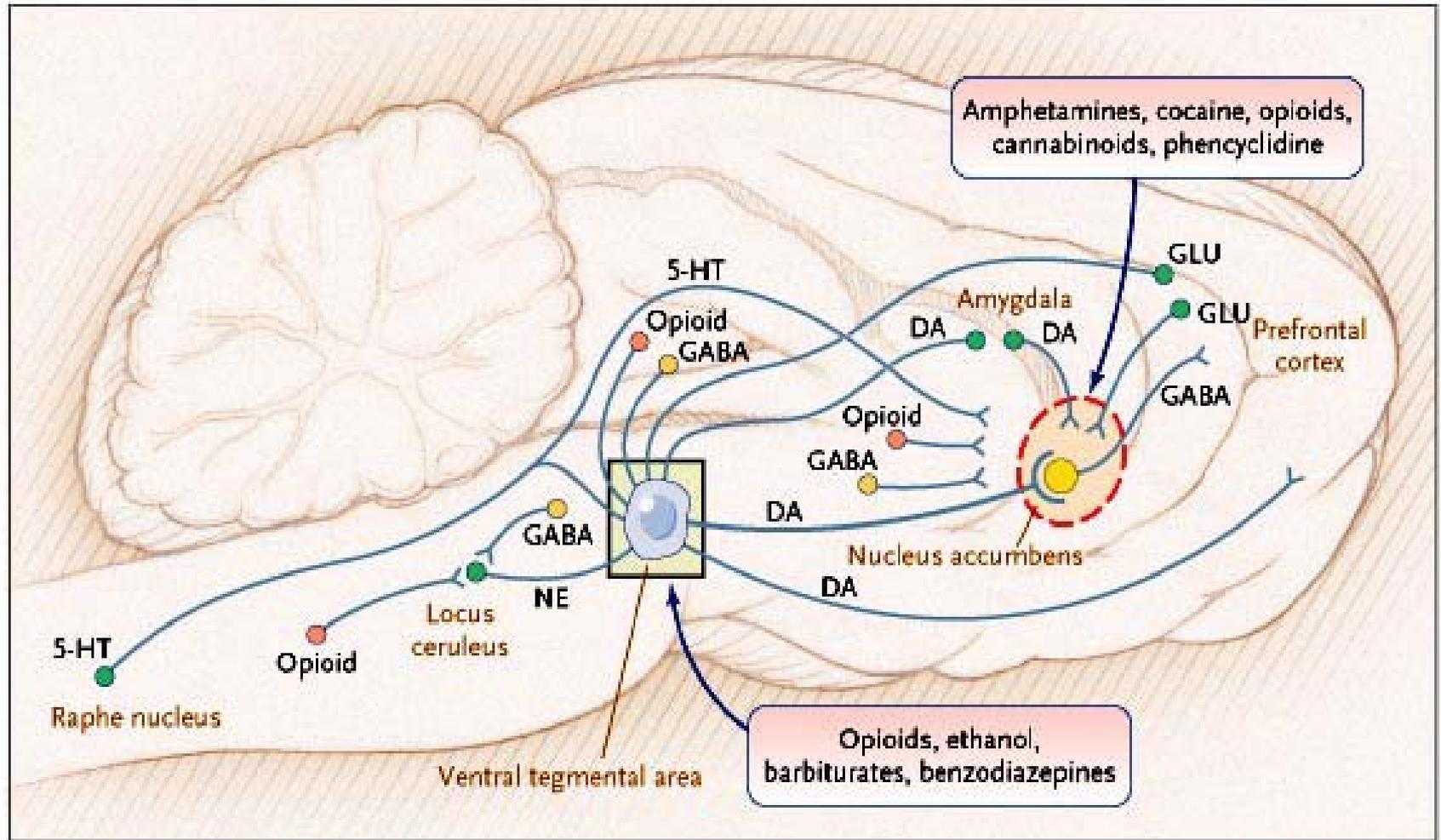


- Responds to dopamine (DA)
- Part of the LIZARD BRAIN
- Responds to drugs
- Responds to food
- Responds to sex
- Responds to gambling
- Sends signals to your frontal cortex
- **THE PLEASURE CENTER IS ABNORMAL (DAMAGED) IN ADDICTION**

# FRONTAL CORTEX-STOP!



# WHO'S IN CHARGE HERE?



# **DOPAMINE (DA) TONE**

- **A-1-allele of the Dopamine D2 Receptor Gene found in around one-third of US population making them susceptible to alcohol and drug addiction, pathological gambling and other addictions**

# **DOPAMINE (DA) TONE**

- **PRODUCT OF THE AMOUNT OF DA RELEASED AT SYNAPSE**
- **PLUS THE NUMBER OF DA RECEPTORS AVAILABLE**
- **PLUS THE AMOUNT OF TIME DA IS AVAILABLE TO THE RECEPTOR AT THE SYNAPSE**
  - **ENZYMATIC BREAKDOWN**
  - **REUPTAKE**
- **Wetsman, Howard. Questions and Answers On Addiction. Rush Press, Lafayette, LA, 2007.**

# DOPAMINE (DA) TONE

- **NUMBER OF DA RECEPTORS**

- IN CHRONIC USE TOTAL NUMBER MAY GO DOWN

- HOWEVER IT HAS BEEN PROPOSED THAT THE STRIATUM MAY BECOME MORE SENSITIVE TO DOPAMINE

- THIS IS ACCOMPLISHED BY MAKING SOME DA RECEPTORS MORE SENSITIVE AND RESPONSIVE

- DOPAMINE RECEPTORS CAN CHANGE BACK AND FORTH BETWEEN TWO STATES

- **HIGH AFFINITY STATE (D2HIGH) –RESPONSIVE**

- BRIAND, ET AL. "COCAINE SELF-ADMINISTRATION PRODUCES A PERSISTENT INCREASE IN D2HIGH RECEPTORS. *EUROPEAN NEUROPSYCHOPHARMACOLOGY*. 18(8):551-556, 2008.

# DOPAMINE (DA) TONE

- **SUFFICIENT**
  - DA TONE IN REWARD CIRCUITRY YIELDS ADEQUATE
    - ATTENTION
    - MOTIVATION
    - ATTACHMENT
    - HEDONIC TONE

# DOPAMINE (DA) TONE

- **REDUCED OR LOW DA TONE**
  - ANHEDONIC RELATIVE TO THOSE AROUND THE INDIVIDUAL
  - SENSE OF NOT FITTING IN
  - POOR ATTENTION
  - POOR LEVEL OF MOTIVATION
  - RESTLESS
  - IRRITABLE
  - DISCONTENTED

# DOPAMINE (DA) TONE

- **REDUCED OR LOW DA TONE (CONTINUED)**
  - **EXAMPLE: PARKINSONS DISEASE**
    - IN TREATED PATIENTS GAMBLING PROBLEMS OCCUR AT 2-4 TIMES RATE OF GENERAL POPULATION
    - GAMBLING PROBLEMS TEND TO APPEAR IN YOUNGER PATIENTS WITH EARLY-ONSET PARKINSONS
    - MANY HAVE PERSONAL AND/OR FAMILY HISTORY OF ALCOHOLISM
    - DA AGONISTS SUCH AS PRAMIPEXOLE (MIRAPEX) AND ROPINIROLE (REQUIP) MAY BE MORE LIKELY THAN LEVODOPA TO INDUCE GAMBLING BEHAVIOR

# DOPAMINE (DA) TONE

- **REDUCED OR LOW DA TONE (CONTINUED)**
    - **EXAMPLE: PARKINSONS DISEASE**
      - **OTHER IMPULSE CONTROL PROBLEMS SUCH AS HYPERSEXUALITY, COMPULSIVE SHOPPING AND UNCONTROLLED EATING CAN EMERGE**
      - **CONSIDER LOWERING DOSE OR SWITCHING MED**
        - **ATYPICAL ANTIPSYCHOTICS WHICH CAN SELECTIVELY BLOCK DA RECEPTORS (NEED TO CLOSELY MONITOR AS CAN AGGRAVATE OTHER SYMPTOMS)**
        - **DEEP BRAIN STIMULATION**
- HARVARD MENTAL HEALTH LETTER, VOL 25, NO 4, OCTOBER 2008, PG 8.**

# **DOPAMINE (DA) TONE**

- **ELEVATED OR HIGH LEVEL OF DA TONE**
  - **WORRY**
  - **ANXIETY**
  - **PERSONAL OR FAMILY HISTORY OF:**
    - **PANIC DISORDER**
    - **OCD**
    - **TICS**
    - **STUTTERING**
  - **MAY USE ALCOHOL TO CALM VIA GABA PATHWAYS BUT WILL GET INCREASED DA WHICH CAUSES DOWN REGULATION OVER TIME AND LOWERED MIDBRAIN DA TONE**

# **DOPAMINE (DA) TONE**

- **PATIENT WILL FIND DRUG(S) THAT ALLOW THEM TO IMPROVE DA TONE**
- **WHAT WAS THEIR FIRST DRUG OF CHOICE (DOC)?**
- **WHAT DID THEY DO BEFORE THAT?**
  - **SPENDING**
  - **SUGAR**
  - **MANIPULATING OTHERS**
  - **TV**
  - **GAMBLING**
  - **OVEREATING**
  - **HYPERSEXUAL ACTIVITY**
  - **OVER-SLEEPING**

# **DOPAMINE (DA) TONE**

- **EXAMPLE:WHAT DO THEY USE TO RELIEVE MIDBRAIN SYMPTOMS OF ADDICTION?**
  - **PT. STATES THE SHE USES DRUG TO REDUCE SYMPTOMS OF ANXIETY**
    - **IS THE DRUG MAKING HER FEEL LESS WORRIED AND/OR PANICKY?**
      - **NORMAL OR HIGH DA TONE**
    - **IS THE DRUG MAKING HER FEEL LESS RESTLESS AND IRRITABLE?**
      - **LOW DA TONE**

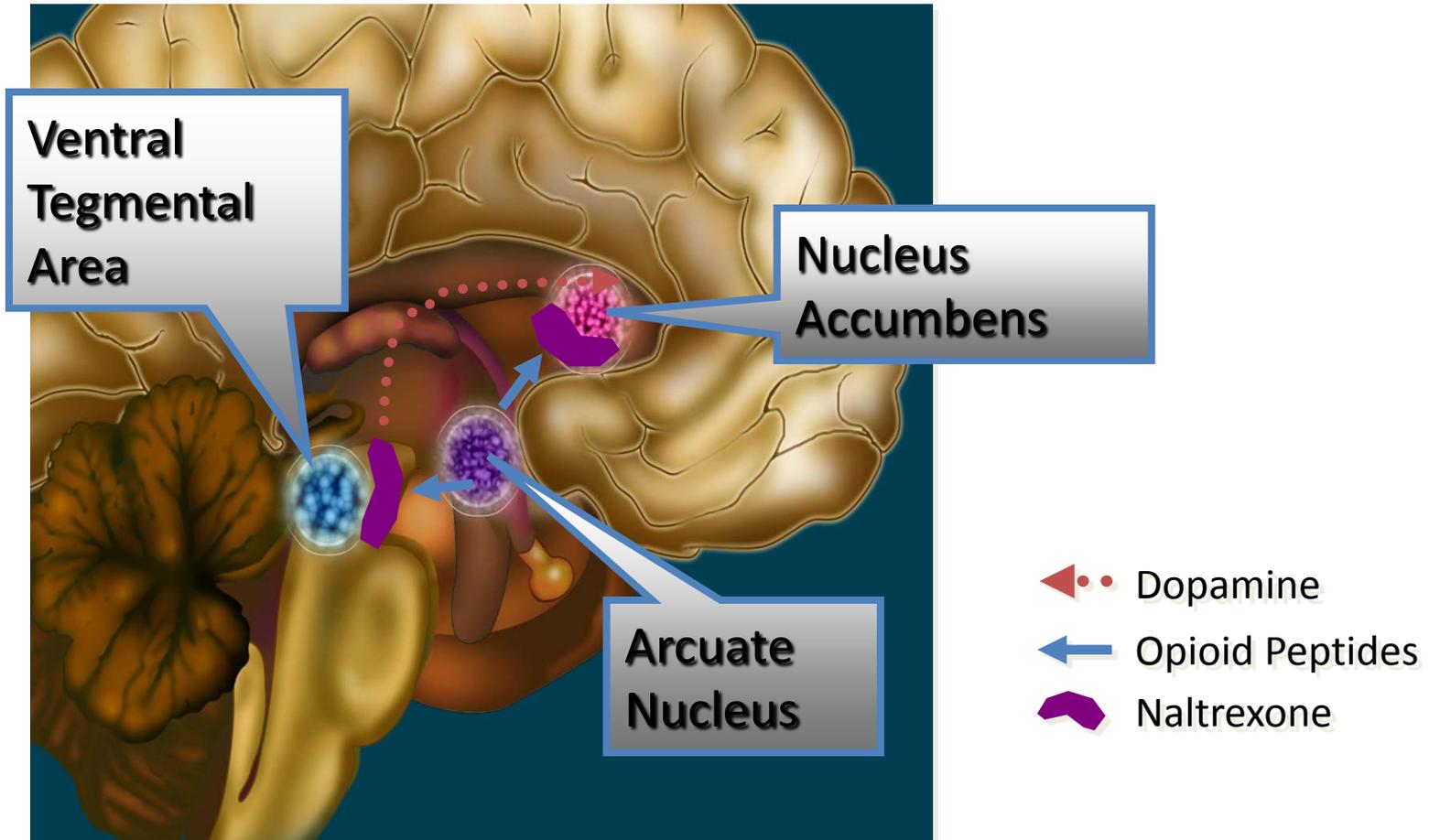
# **DOPAMINE (DA) TONE**

- **EXAMPLE:WHAT DO THEY USE TO RELIEVE MIDBRAIN SYMPTOMS OF ADDICTION?**
  - **PT STATES HE USES DRUG TO REDUCE THE SYMPTOMS OF DEPRESSION THAT ARE OVERWHELMING.**
    - **LOW DA TONE SECONDARY TO SUBSTANCE ABUSE**
      - » **ANHEDONIA**
      - » **IRRITABILITY**
      - » **POOR MEMORY**
      - » **POOR LEVEL OF MOTIVATION**
      - » **POOR LEVEL OF ATTENTION**
      - » **FATIGUE**
      - » **FEELINGS OF EMPTINESS**
    - **IF TRUE CLINICAL DEPRESSION SSRI'S WOULD HELP OVER THE LONG HAUL BUT IF SECONDARY TO SUBSTANCE USE THE SSRI'S WOULD LOWER DA TONE AND WOULD SEE WORSENING OF SYMPTOMS**

# **DOPAMINE (DA) TONE**

- **TWO TYPES OF LOW DA TONE**
  - **DA RECEPTOR SIGNAL AT NUCLEUS ACCUMBENS (NAc)**
  - **OPIOID RECEPTOR SIGNAL AT VENTRAL TEGMENTAL AREA (VTA)**
- **CAN INVOLVE ANY PART OF MECHANISM FOR SIGNAL CONDUCTION**
- **TWO NEUROTRANSMITTER SYSTEMS FORM A POSITIVE FEEDBACK LOOP, EACH CAUSES AN INCREASE IN THE OTHER**
  - **WHEN NOT FUNCTIONING PROPERLY GET LESS THAN NORMAL HEDONIC RESPONSE TO STIMULI**

# Reward Pathways



# **DOPAMINE (DA) TONE**

- **TWO TYPES OF LOW DA TONE (CONTINUED)**
- **SYMPTOMS WILL BE THOSE OF REDUCED DA TONE AT NAc REGARDLESS OF THE LOCATION OF FEEDBACK PROBLEM**
- **FROM TREATMENT PERSPECTIVE WHAT DIFFERENTIATES WHETHER DA OR OPIOID CAUSATION OF LOW DA TONE IS....**
  - **HISTORY OF DRUG USAGE AND EFFECTS THAT USER EXPERIENCES**

# **DOPAMINE (DA) TONE**

- **DA RECEPTOR SIGNAL AT NAc**
  - **COULD HAVE NORMAL FUNCTIONING VTA AND NORMAL FUNCTIONING OPIOID RECEPTOR ON VTA**
    - **LIKE DRUGS THAT CAUSE DIRECT INCREASE IN DA AT THE NAc OR DIRECTLY STIMULATE THE NAc**
    - **DRUGS ACTING ON OPIOID RECEPTOR WILL NOT PROVIDE MUCH OF A REWARD BECAUSE SYSTEM IS FUNCTIONING NORMALLY**
    - **MAY USE OPIOIDS BUT AT BEST WILL BE A SECOND CHOICE**
    - **DOC WILL BE STIMULANTS OF ALL TYPES INCLUDING NICOTINE**

# **DOPAMINE (DA) TONE**

- **OPIOID RECEPTOR SIGNAL AT VTA**
  - **DRUGS THAT INCREASE DA NOT AS EFFECTIVE**
  - **DOC ARE OPIOID AGONISTS**
  - **COCAINE DOESN'T WORK VERY WELL UNLESS COMBINED WITH OPIOID**
  - **METHAMPHETAMINE CAUSES ADDITIONAL RELEASE OF DA AT NAc RATHER THAN JUST REUPTAKE INHIBITION (MIMICS THE EFFECT OF OPIOID), NICOTINE STIMULATES DA RELEASE**
    - **PT. MAY STATE THAT LIKES METH AND COKE DOESN'T WORK VERY WELL**

# **DOPAMINE (DA) TONE**

- **COULD HAVE BOTH TYPES OF REDUCED DA TONE (DA AND OPIOID)**
  - **OCCURS IN APPROXIMATELY ONE-HALF OF OPIOID DEPENDENT PTS**
    - **IF GIVE THEM BUPRENORPHINE MAY CONTINUE TO SMOKE OR SMOKE MORE**
      - **VTA MAKES MORE DA SO SMOKING IS MORE REWARDING**
        - » **EVIDENCE OF LOW DA TONE**

# Dopamine D2 Receptors are Lower in Addiction



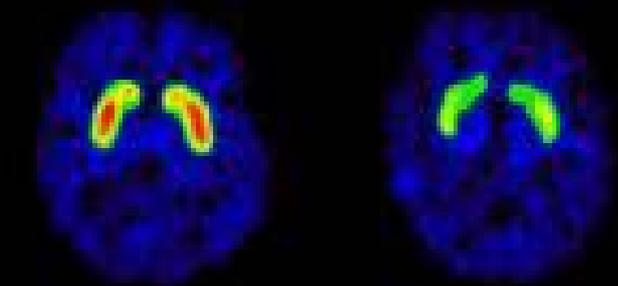
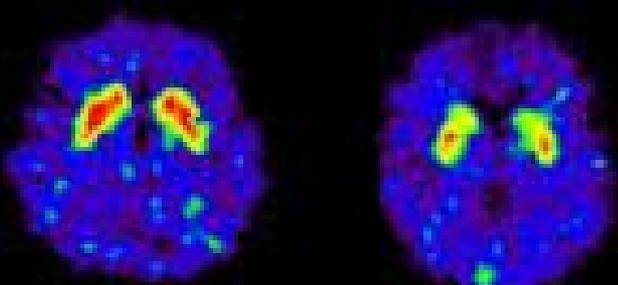
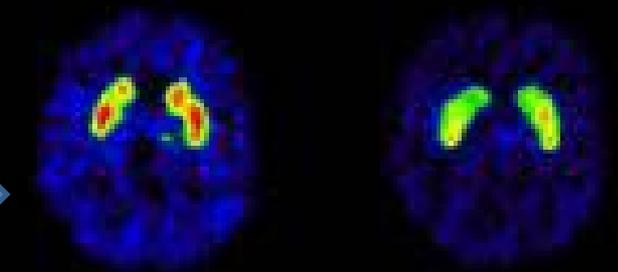
Cocaine



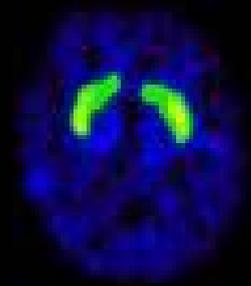
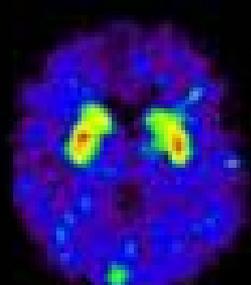
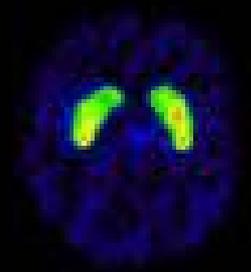
Alcohol



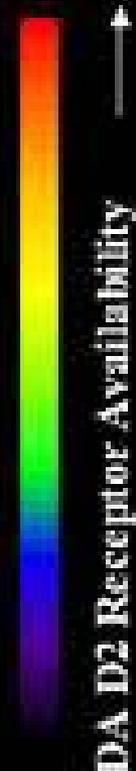
Heroin



control



addicted



DA D2 Receptor Availability



Reward Circuits  
*Non-Drug Abuser*



Reward Circuits  
*Drug Abuser*

# Dopamine D2 Receptors are Lower in Addiction



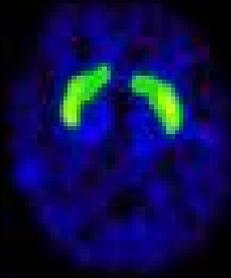
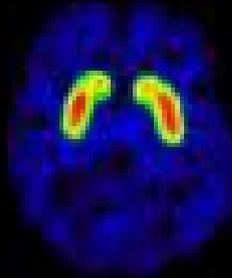
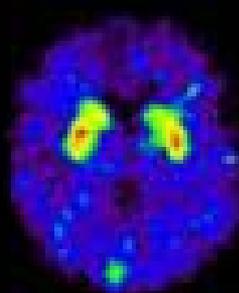
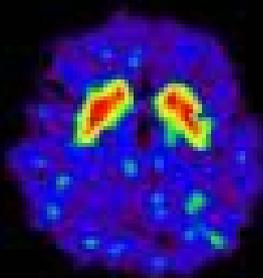
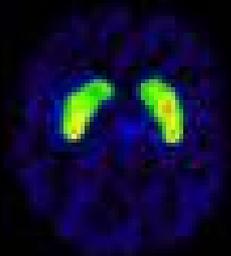
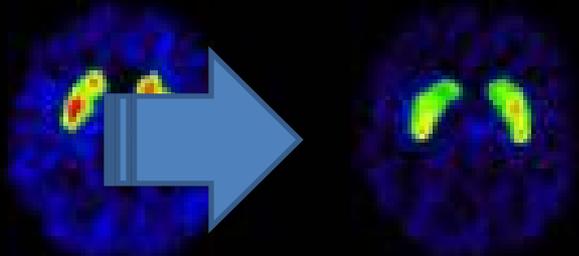
Cocaine



Alcohol

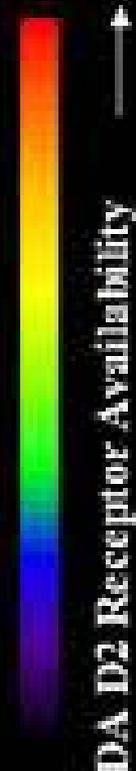


Heroin



control

addicted



DA D2 Receptor Availability



*Non-Drug Abuser*



*Drug Abuser*

# Dopamine D2 Receptors are Lower in Addiction



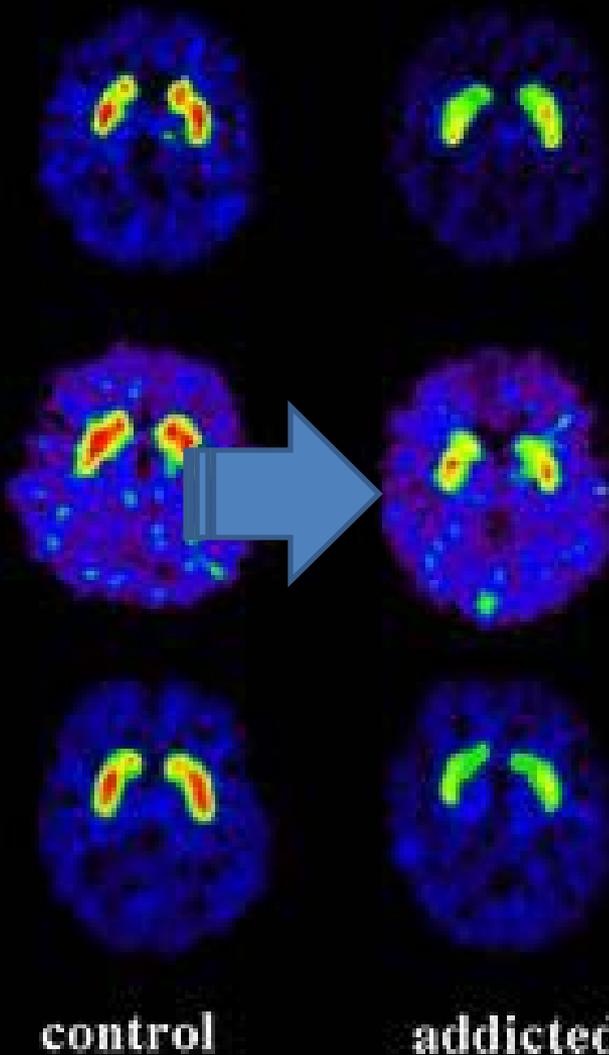
Cocaine



Alcohol



Heroin



DA D2 Receptor Availability ↑



Reward Circuits  
*Non-Drug Abuser*



Reward Circuits  
*Drug Abuser*

# Dopamine D2 Receptors are Lower in Addiction



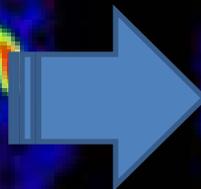
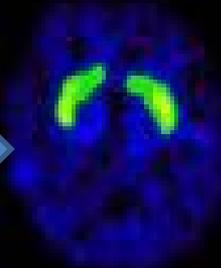
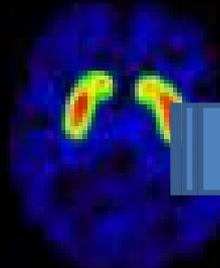
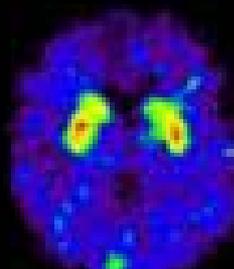
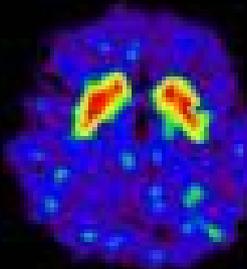
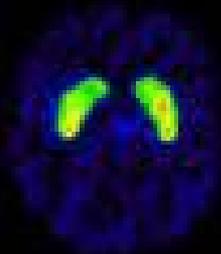
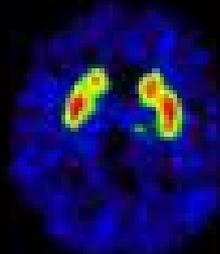
Cocaine



Alcohol

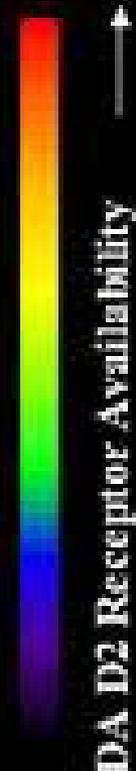


Heroin



control

addicted



DA D2 Receptor Availability



Reward Circuits  
*Non-Drug Abuser*



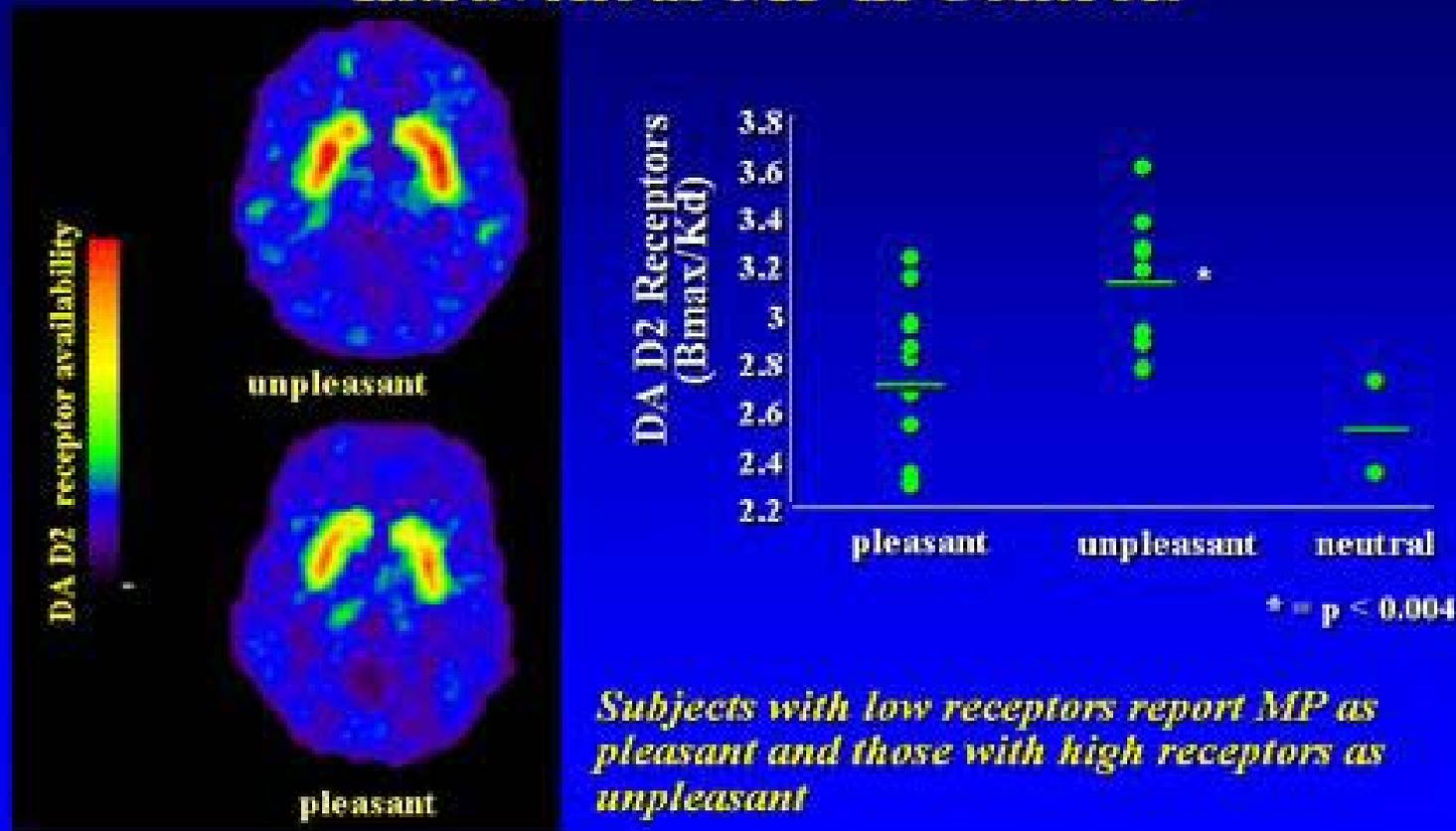
Reward Circuits  
*Drug Abuser*

# **Which came first?**

- **Do some people develop addiction because they have “reward deficiency syndrome” (decreased dopamine) OR:**
- **Do people with addiction have low dopamine because they have “burned out” their pleasure centers?**

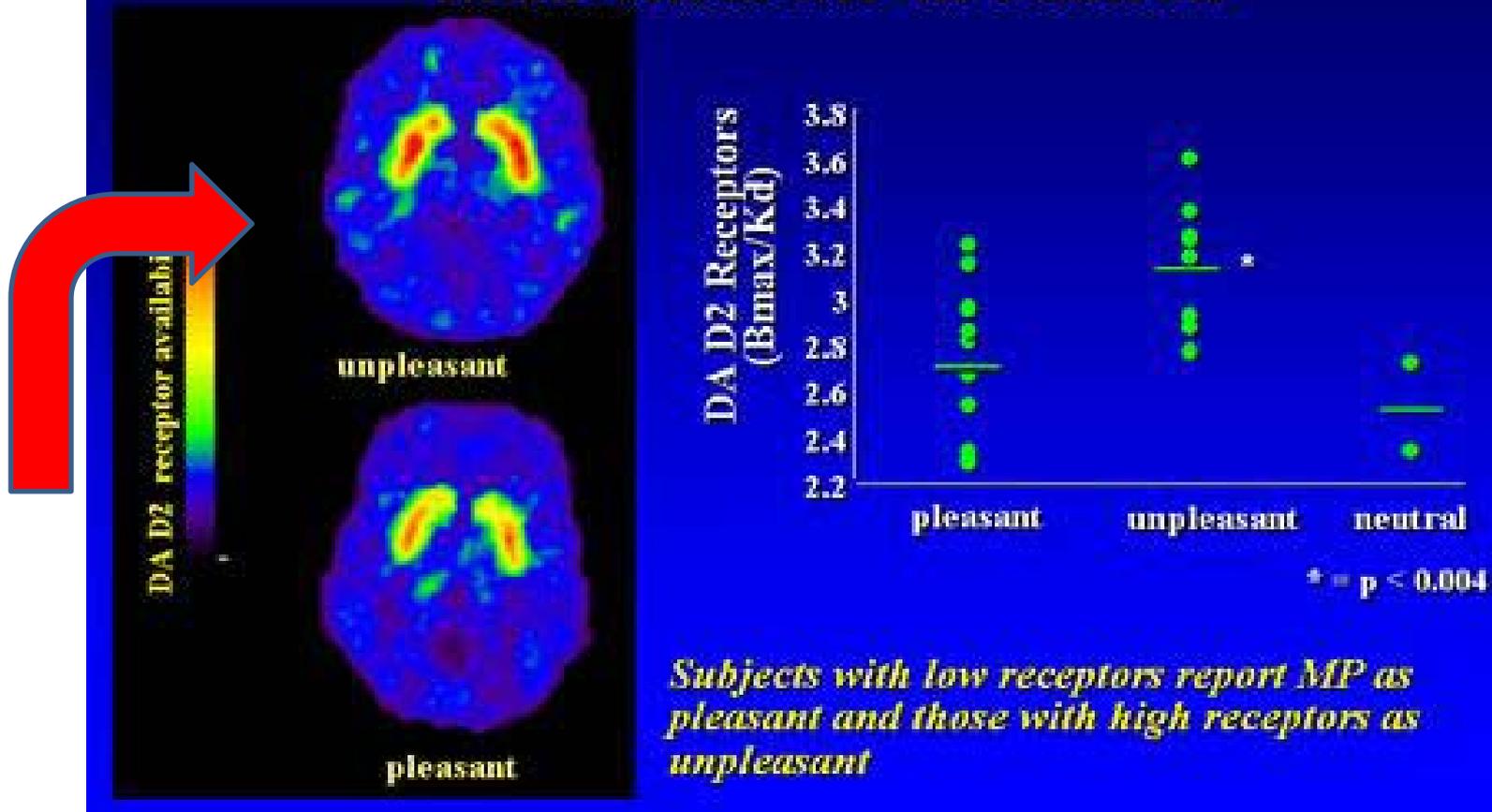
# Abnormal response to Ritalin (methylphenidate) is due to abnormal brain chemistry

## DA D2 Receptors and Response to Intravenous MP in Controls



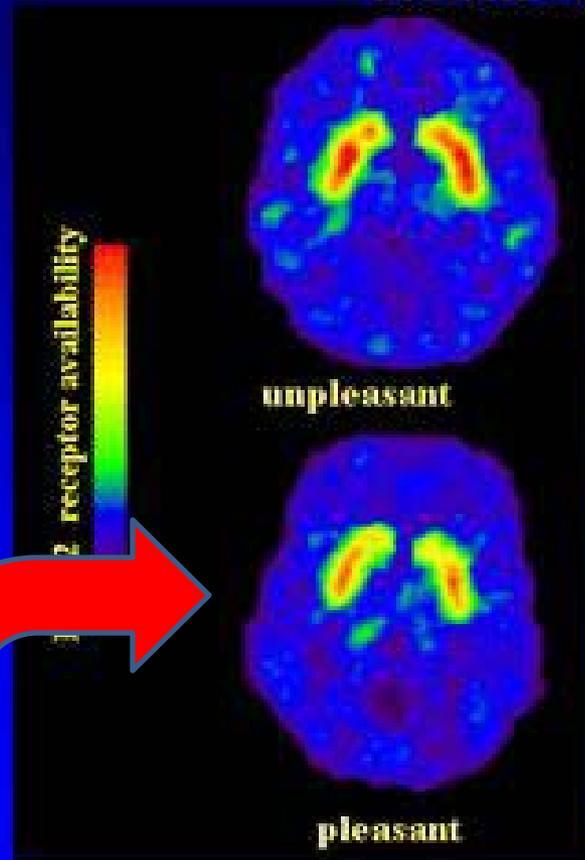
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## DA D2 Receptors and Response to Intravenous MP in Controls



# Abnormal response to Ritalin (methylphenidate) is due to abnormal brain chemistry

## DA D2 Receptors and Response to Intravenous MP in Controls



DA D2 Receptors  
(Bmax/Kd)

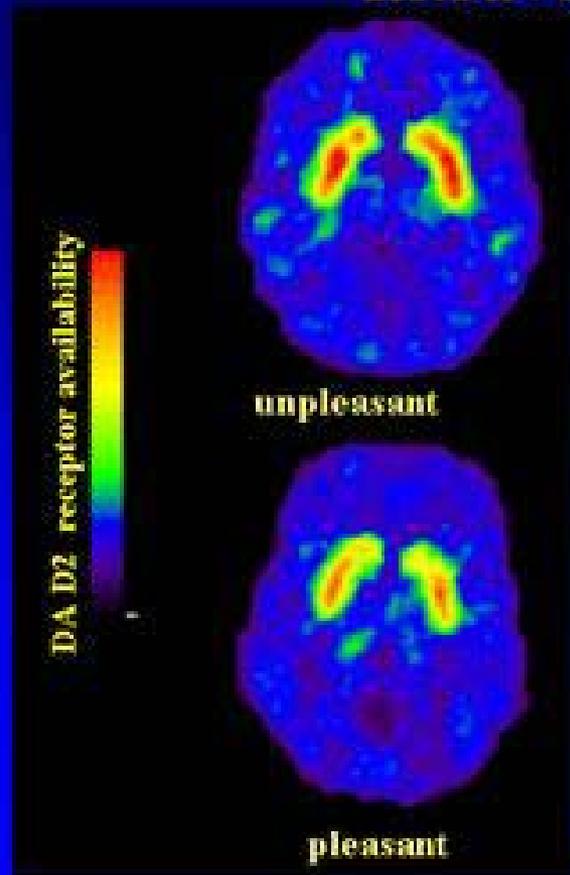


\* =  $p < 0.004$

*Subjects with low receptors report MP as pleasant and those with high receptors as unpleasant*

# Abnormal response to Ritalin (methylphenidate) is due to abnormal brain chemistry

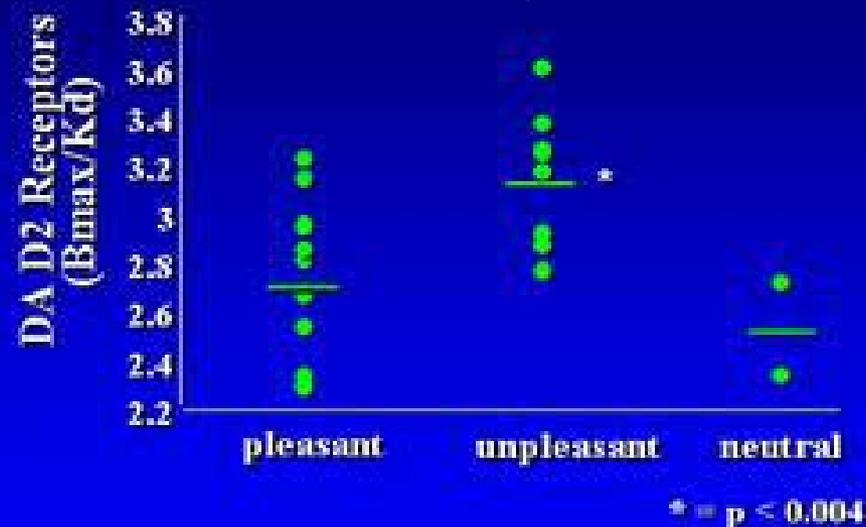
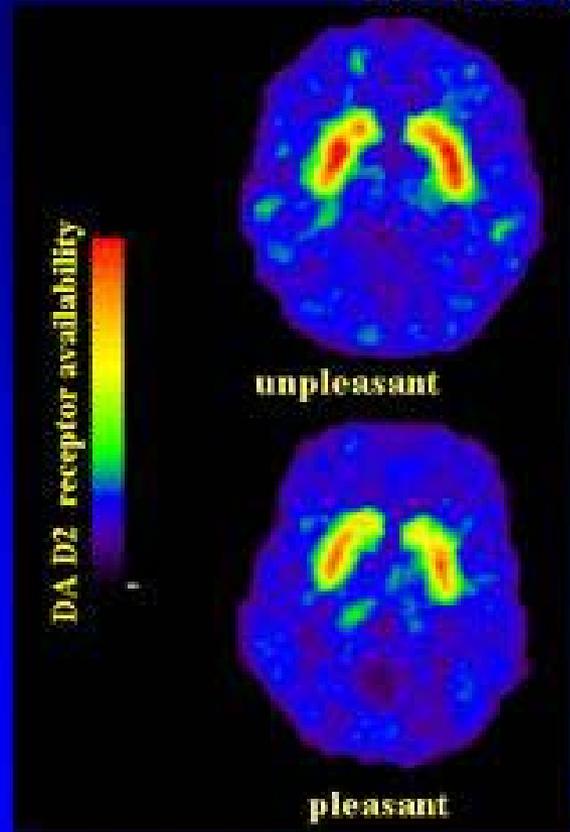
## DA D2 Receptors and Response to Intravenous MP in Controls



*Subjects with low receptors report MP as pleasant and those with high receptors as unpleasant*

# Abnormal response to Ritalin (methylphenidate) is due to abnormal brain chemistry

## DA D2 Receptors and Response to Intravenous MP in Controls



*Subjects with low receptors report MP as pleasant and those with high receptors as unpleasant*

# Can you find the (alleged) future alcoholic?



# Decreased “hedonic tone”



# **DOPAMINE (DA) TONE**

- **NOTION THAT ADDICTION EQUALS TOO MUCH DOPAMINE IS A GROSS OVERSIMPLIFICATION**
- **IN ANIMAL STUDIES**
  - **EVEN WHEN DA RECEPTORS ARE BLOCKED SOME DRUG-SEEKING BEHAVIOR PERSISTS**
    - **EXTERNAL CUE DRIVEN**
  - **DRUGS AFFECTING DA DIRECTLY HAVE BEEN INEFFECTIVE**
  - **INDIRECT APPROACHS SUCH AS INCREASING GABA EFFECT AND REDUCING GLUTAMATE EFFECT SEEM MORE PROMISING (EXAMPLE-TOPIRIMATE)**

**BRAIN WORKS. VOL 18, NO 5, SEPT/OCT 2008, PGS 1 AND 2.**

# **RESTORING DOPAMINE BALANCE**

- **MORE TO THE PICTURE THAN JUST DOPAMINE**
- **IN ANIMAL STUDIES, EVEN WHEN DOPAMINE RECEPTORS ARE BLOCKED, SOME DRUG-SEEKING BEHAVIORS PERSIST**
  - PPT
- **DRUGS THAT AFFECT DOPAMINE DIRECTLY HAVE BEEN INEFFECTIVE IN CLINICAL TRIALS**
- **THOSE THAT ACT INDIRECTLY HAVE BEEN MORE PROMISING**

# **ADDICTION AND RECOVERY**

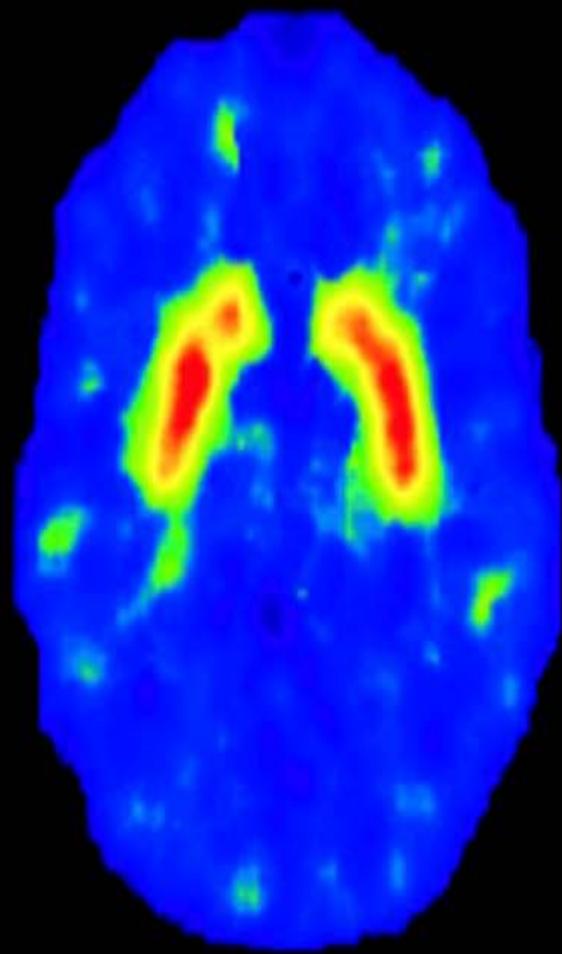
- **CHANGES IN BRAIN GLUTAMATE SIGNALING INDUCED BY CHRONIC DRUG EXPOSURE HAS A WIDE VARIETY OF NEUROBIOLOGICAL EFFECTS INSTRUMENTAL IN THE TRANSITION FROM DRUG ABUSE TO ADDICTION (KAVALIS,2009)**
- **THESE NEURAL ALTERATIONS LIMIT THE ABILITY TO ADAPT TO NEW INFORMATION (TO STOP TAKING DRUGS IN SPITE OF ADVERSE CONSEQUENCES)AND STRENGHTEN THE POWER OF DRUG LEARNED ASSOCIATIONS**

# **ADDICTION AND RECOVERY**

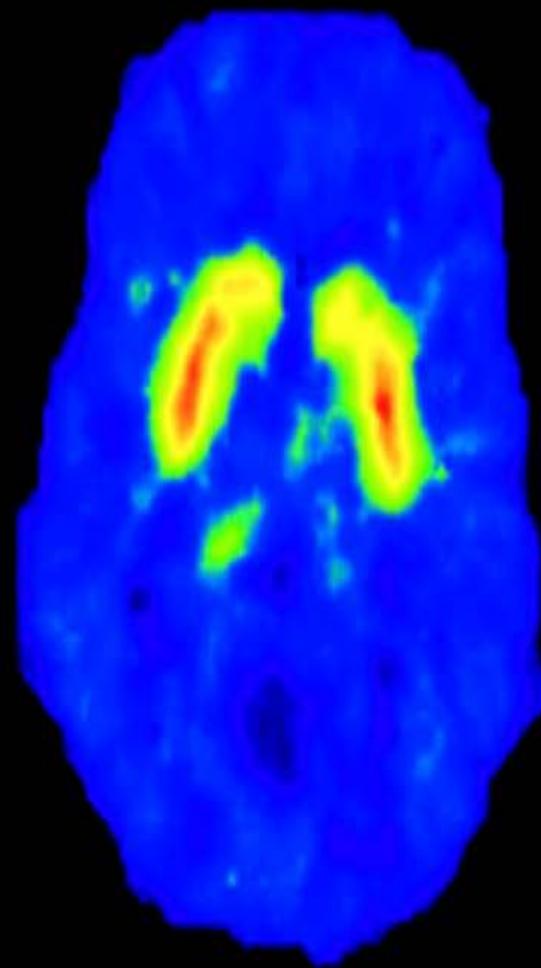
- **COMPULSION SUPPLANTS PLEASURE AS THE PRIMARY MOTIVATION FOR CONTINUED DRUG USE, GLUTAMATE RATHER THAN DOPAMINE BECOMES THE NEUROTRANSMITTER CLOSELY TIED TO DRUG-SEEKING**
- **GLUTAMATE IMBALANCE IMPLICATED IN THE HYPERRESPONSIVENESS TO DRUG-CUES**

# **ADDICTION AND RECOVERY**

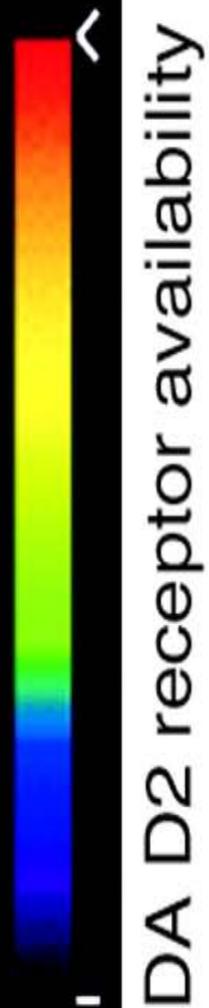
- **RESEARCH IMPLICATING GLUTAMATE AS A FINAL COMMON PATHWAY FOR DRUGS OF ADDICTION HIGHLIGHT ITS THERAPEUTIC POTENTIAL**
- **SEVERAL MEDICATIONS ARE INVOLVED IN NIDA FUNDED TRIALS**
  - **GOAL IS TO NORMALIZE GLUTAMATE LEVELS**
    - **ACETYLCYSTEINE-PULMONARY DISEASE AND ACETAMINOPHEN OVERDOSE**
    - **CEFTRIAXONE-ANTIBIOTIC**
  - **Volkow and Kalivas. The Neural Basis of Addiction: A Pathology of Motivation and Choice. *AM J Psychiatry*, 162:8, August 2005, pgs. 1403-13**



High receptor level  
unpleasant response



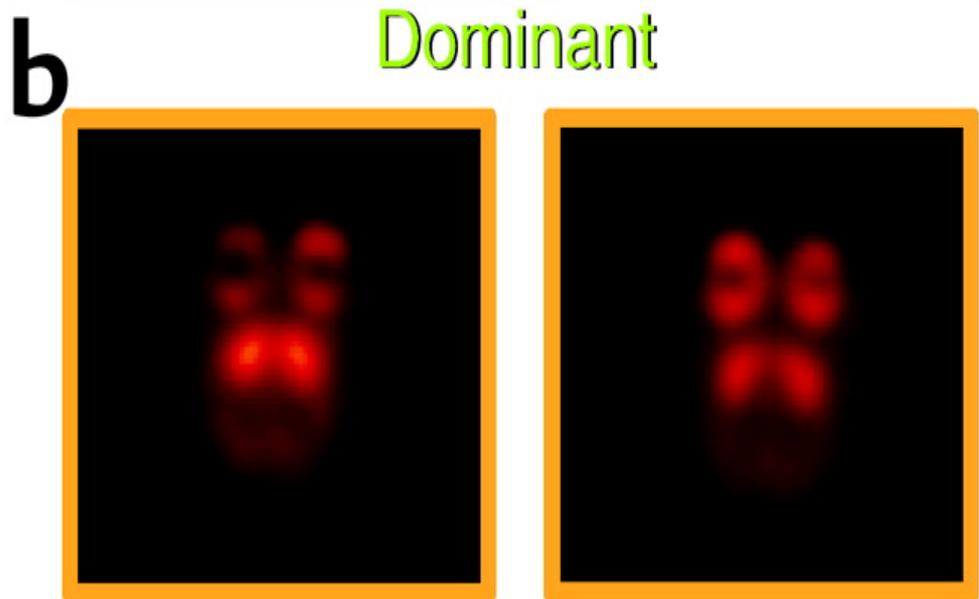
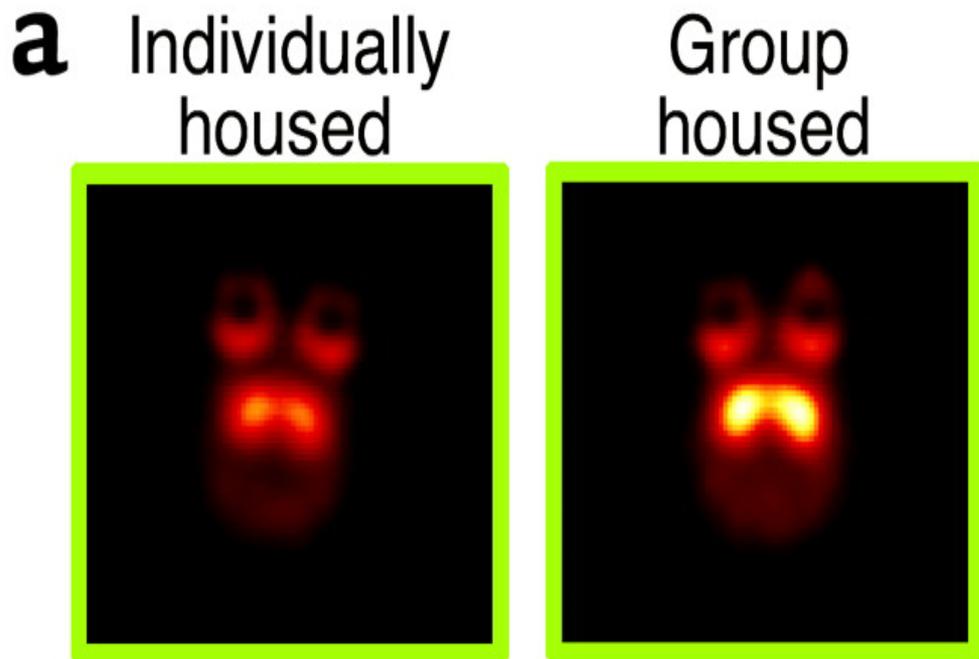
Low receptor level  
pleasant response



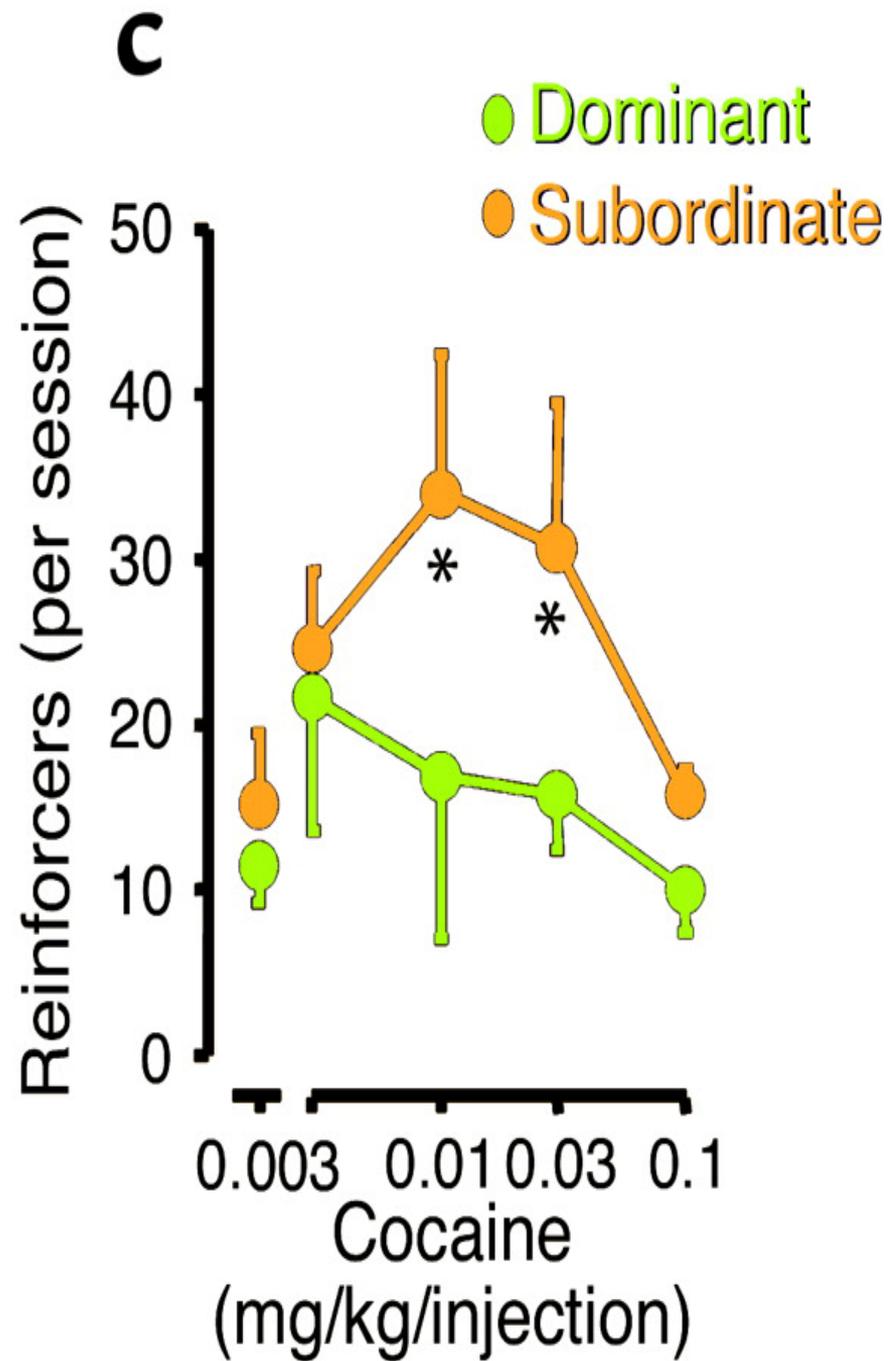
DA D2 receptor availability

# DOPAMINE D2 RECEPTORS

- Association between DA D2 receptor numbers and drug self-administration (PET)
  - Increased D2 receptors reduced alcohol consumption
  - Decreased D2 receptors higher risk
- *DA D2 receptor levels influenced by stress and social hierarchy*
- STRESS CAN PRECIPITATE ANTIREWARD SYMPTOMS
- <http://dionysus.psych.wisc.edu/lit/articles/VolkowN1993a.pdf>
- <http://www.mc.vanderbilt.edu/reporter/index.html?ID=2583>



Subordinate



# ENVIRONMENT AND SOCIAL STATUS

- Subordinate animals more likely to self-administer cocaine
- Dominant animals no more likely to self-administer cocaine than placebo
- ***Social interventions can change neurobiology***
  - Increased DA D2 receptors
  - Reduced self-administration
- ***Behavioral interventions could counteract the aversive effects of drug abuse and reinforce the power of group approaches***

# INTUITIVE INSIGHT

- **ARCHIMEDES IN THE BATH (CALCULATE DENSITY AND VOLUME)**
- **DESCARTES IN BED WATCHING FLIES ON CEILING (COORDINATE GEOMETRY)**
- **NEWTON WHEN HE SAY AN APPLE FALL (LAW OF UNIVERSAL GRAVITY)**
- **“AHA” OR EPIPHANY**

# **“AHA” OR EPIPHANY**

- **A SUDDEN COMPREHENSION THAT ALLOWS YOU TO SEE SOMETHING IN A DIFFERENT WAY**
- **REQUIRES MORE NEURAL RESOURCES THAT METHODOLOGICAL THINKING**
- **FACILITATED BY A POSITIVE MOOD**
- **DAYDREAMING**

# **DAYDREAMING**

- **ONE-THIRD OF THE TIME**
- **INVOLVES SEVERAL NEURAL AREAS ASSOCIATED WITH COMPLEX PROBLEM SOLVING**
- **ONLY TIME THESE AREAS WORK IN UNISON**

# **INSIGHT (INTUITIVE)**

- **FLASH OF GAMMA WAVES EMANATING FROM RIGHT HEMISPHERE**
  - **HANDLES ASSOCIATIONS**
  - **ASSEMBLES ELEMENTS OF A PROBLEM**
- **BRAIN BROADCASTS THE SIGNAL ONE-THIRD OF A SECOND PRIOR TO CONSCIOUS MOMENT OF INSIGHT**

# **INSIGHT (INTUITIVE)**

- **PATTERNS OF HIGH FREQUENCY NEURAL ACTIVITY IN RIGHT FRONTAL CORTEX THAT IDENTIFIES WHO WILL SOLVE PROBLEM BY INSIGHT AND WHO WOULD NOT**
- **INSIGHT FAVORS A PREPARED MIND**
- **CREATIVE THOUGHT IS A PRODUCT OF NEURONS AND NERVE CHEMISTRY OUTSIDE OF AWARENESS AND BEYOND ONES DIRECT CONTROL**

# **INSIGHT (INTUITIVE)**

- **LEFT HEMISPHERIC DECISION MAKING**
  - **DRAWS FROM OUR MEMORY (PAST)**
  - **FUNCTIONS IN A REDUCTIONISTIC FASHION**
    - **LIKES TO LABEL**
    - **REDUCE TO SMALLEST ELEMENT**
    - **SEES THE TREE BUT MISSES THE FOREST**
  - **PROCESSES SLOWLY**
  - **GIVES AN EXPLICIT RESPONSE (ANSWER)**

# **INSIGHT (INTUITIVE)**

- **RIGHT HEMISPHERE DECISION MAKING**
  - **DRAWS FROM IMPLICIT, UNCONSCIOUS MIND (90%) , AFFECT AND THE FIELD OF CONSCIOUSNESS (BASED UPON ONE'S LEVEL OF SPIRITUAL CONSCIOUSNESS)**
  - **HOLISTIC AND FAST**
  - **GIVES AN IMPLICIT, INTUITIVE RESPONSE RESULTING IN A WORLDVIEW CHANGE**

**NOTE: EMOTIONAL SYSTEM MIGHT EXCELL AT COMPLEX DECISIONS AND THE UNCONSCIOUS IS BETTER SUITED FOR DIFFICULT COGNITIVE TASKS**

# **LEARNING AND MEMORY**

- **EXTERNAL INTERFACE BETWEEN SELF AND ENVIRONMENT**
  - **SENSE CAN BE THOUGHT OF AS SOCIAL WINDOW THROUGH WHICH THE BRAIN CAN SAMPLE THE EXTERNAL ENVIRONMENT BY DETECTING THE PHYSICAL ATTRIBUTES OF THE WORLD AND ITS OBJECTS**
  - **PERCEIVED INFORMATION IS QUICKLY ORGANIZED INTO SIGNALS OF NEURONAL IMPULSES AND USED TO CONSTRUCT NEURAL MODELS OF EXTERNAL RELIABILITY**

# LEARNING AND MEMORY

- **EXTERNAL INTERFACE BETWEEN SELF AND ENVIRONMENT (CONTINUED)**
  - **CONSTRUCTION OF INTERNAL MAPS OF EXTERNAL SPACE**
  - **CREATION OF INTERNAL MAPS ALLOWS ACTION SELECTION BASED ON MULTIPLE INTERNAL AND EXTERNAL CIRCUMSTANCES**
    - **DETAILED NEURAL MAPS ARE COMBINED WITH DYNAMIC SELF-REPRESENTATIONS, GENETICALLY PREPROGRAMMED AND LEARNED ORGANIZING PRINCIPLES AND PERTINENT SETS OF REMEMBERED RULES**
  - **FROM THIS COMPLEX ARRAY OF INTEGRATED INFORMATION, BEHAVIORAL PROGRAMS THAT ADDRESS EXTERNAL AND INTERNAL DEMAND CAN BE GENERATED**

**VIAMONTES. SIGNAL TRANSDUCTION IN PSYCHIATRY. PSYCHIATRIC ANNALS, VOL 38, NO 4, APRIL 2008.**



# **ADDICTION: DYSFUNCTION IN LEARNING AND MEMORY**

- **TWO DA SYSTEMS IN MAMMALIAN FOREBRAIN**
  - **SUBSTANCIA NIGRA-PROVIDES DA TO DORSAL STRIATUM (CAUDATE-PUTAMAN) AS PART OF EXTRAPYRAMIDAL MOTOR SYSTEM**
  - **REMAINDER OF FOREBRAIN (AMYGDALA, PFC, NAc) RECEIVES DOPAMINERGIC PROJECTIONS FROM VTA**

# **ADDICTION: DYSFUNCTION IN LEARNING AND MEMORY**

- **NATURAL REWARD STIMULI CAUSES INCREASED FIRING IN VTA WITH DA RELEASE IN PFC, AMYGDALA AND NAc**
- **WHEN REWARD BECOMES PREDICTABLE, THE INCREASE IN VTA NEURONAL FIRING AND DA RELEASE CEASES IN RESPONSE TO THE REWARDING STIMULI AND IS ONLY EVOKED BY THE CONDITIONED CUE**
- **DA SECRETED ONLY AS LONG AS THE BEHAVIOR IS IN LEARNING CURVE**

# **ADDICTION: DYSFUNCTION IN LEARNING AND MEMORY**

- **ALCOHOL/DRUGS INCREASE DA JUST LIKE  
NATURAL REWARD STIMULI**
- **EACH DRUG WORKS THRU DIFFERENT  
MECHANISM IN THE PATHWAY**
  - **COCAINE-BLOCKS DA REUPTAKE TRANSPORTER**
  - **METHAMPHETAMINE-REVERSES THE  
TRANSPORTER PROCESS**
  - **HEROIN, ALCOHOL-VTA BY REMOVING  
INHIBITION THAT NORMALLY REDUCES ACTIVITY**

# **ADDICTION: DYSFUNCTION IN LEARNING AND MEMORY**

- **UNLIKE NATURAL STIMULI, THESE DRUGS WITH REPEATED EXPOSURE CONSISTENTLY PRODUCE LARGE INCREASES IN DA WITH EACH ADMINISTRATION**
- **CREATES AN “OVER-LEARNING” PROCESS IN REGARD TO MOTIVATIONAL BEHAVIORS AND CUES**

# **ADDICTION: DYSFUNCTION IN LEARNING AND MEMORY**

- ***RELAPSE FALLS ALONG A SPECTRUM***



- **COMPULSIVE RELAPSE**
- **PREFRONTAL CORTEX OFF-LINE**

- **REGULATED RELAPSE**
- **SOME PREFRONTAL AVAILABILITY**

- **LITTLE OR NO RELAPSE**
- **PREFRONTAL CORTEX AVAILABLE**

# **ADDICTION: DYSFUNCTION IN LEARNING AND MEMORY**

- ***RELAPSE FALLS ALONG A SPECTRUM  
(CONTINUED)***
  - ***COMPULSIVE RELAPSE***
    - **HABIT LIKE WITH LITTLE COGNITIVE INPUT**
    - **INVOLVES THE DORSAL STRIATUM**
    - **DECISION MAKING OCCURRS AT LEVEL INCAPABLE OF GUIDING BEHAVIOR IN DIRECTION THAT CAN COMPETE WITH DRUG SEEKING AND USING**
    - **PRECONTEMPLATION**
    - **GOAL: MOVE TO RESTORE PFC CONTROL**
      - **ANTICRAVING MEDS**

# **ADDICTION: DYSFUNCTION IN LEARNING AND MEMORY**

- ***RELAPSE FALLS ALONG A SPECTRUM  
(CONTINUED)***

- ***REGULATED RELAPSE***

- **INVOLVES NAc CORE AND INPUTS FROM MEMORY, DECISION-MAKING AND EMOTIONAL STRUCTURES SUCH AS HIPPOCAMPUS, BASOLATERAL AMYGDALA, DORSAL PFC**
- **HABIT-RELATED DORSAL STRIATUM NOT INVOLVED**
- **SINCE PFC HAS NOT GONE OFF-LINE MIGHT BE MORE AMENABLE TO TREATMENT AND COULD BE IN CONTEMPLATION, PREPARATION OR ACTION STAGE**
- **GOAL: GREATER AND GREATER PFC CONTROL AND ABILITY TO MOVE TOWARDS LITTLE OR NO RELAPSE**
- **SUBSTITUTION THERAPIES LIKE SUBOXONE, NICOTINE PATCHES, ETC MAY SERVE AS BRIDGE**

# **ADDICTION: DYSFUNCTION IN LEARNING AND MEMORY**

- ***RELAPSE FALLS ALONG A SPECTRUM  
(CONTINUED)***

- **LITTLE OR NO RELAPSE**

- **LITTLE OR NO DYSFUNCTIONAL CHANGES IN NEURAL CIRCUITRY**
- **DRUG USE PRIMARILY DEPENDENT UPON NATURAL REWARDING AND REINFORCING EFFECTS OF DRUG ON DA SYSTEM**
- **PARTICULARLY THE DA PROJECTIONS INTO NAc**

**LALUMIERE AND KALIVAS. *COCAINE ADDICTION: MECHANISMA OF ACTION*. PSYCHIATRIC ANNALS. VOL 38, NO. 4, APRIL, 2008.**

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